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Electrolyte-Fluid Distribution
in
Acute Uraemia
with and without Overhydration
in
the Rabbit

By

HANS THYSELL

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University of Lund, Sweden.*

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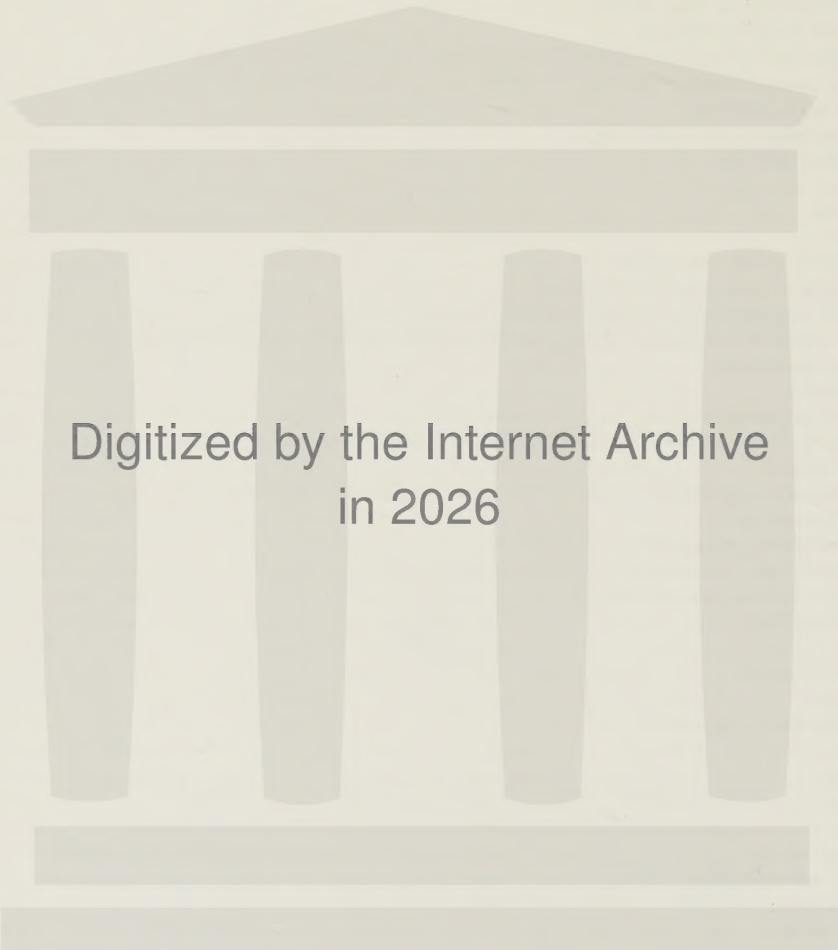
Translated by
James L. Brown



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INTRODUCTION

The clinical prognosis of acute renal failure has radically improved during the last two decades. Increased knowledge and better possibility to prevent and correct the most serious electrolyte-fluid disturbances associated with this condition have contributed to this progress.

Earlier the most common immediate causes of death in such cases were hyperpotassaemia and overhydration (cerebral and pulmonary oedema). Though such serious electrolyte-fluid disturbances have become less common, various electrolyte-fluid disturbances are nonetheless frequently encountered and often difficult to explain.

The electrolyte-fluid disturbances in acute renal

failure have been the subject of numerous studies (for ref. see Maher & Schreiner 1961, Bergström & Bittar 1969, Muehrcke 1969). In these studies interest has been focused mainly on one or a few changes in plasma or tissues in the individual experiment. Further, the investigations vary in respect of the clinical and experimental conditions under which they have been performed. For this reason a more comprehensive study of the electrolyte-fluid disturbances following the acute loss of the kidney function was undertaken. The aim of the present investigation was also to evaluate the effect of nephrectomy combined with overhydration on the electrolyte-fluid distribution, under standardised conditions.

MATERIALS AND METHODS

About 200 white rabbits, 4.5 to 5.5 months old and weighing 1.6–2.6 kg, were used. During at least 14 days before use they were allowed water and food *ad lib* and were observed for any signs of disease. The food consisted of pellets (Fors AB, Malmö, Sweden) containing 13.5% crude protein (10.5% proteins that could be digested with aid of pepsin, 0.8% fish protein), 2.5% crude fat and 13.0% vegetable fibres. The content of Na, K and Cl was 0.10, 0.45 and 0.11 mEq/g. Further the diet contained 11.0% water, 1.4% calcium, 0.6% phosphorus, vitamins and trace elements. The ash weight was 9.0%.

EXPERIMENTAL SERIES

Controls. The controls consisted of 9 rabbits. To enable estimation of the extracellular volume, a standard amount of ^{82}Br and ^{51}Cr -EDTA was injected intravenously. To compensate for the rapid renal elimination of ^{51}Cr -EDTA the animals were thereafter given a continuous infusion of the latter substance until they were killed 12 hours later by an intravenous injection of enibomal sodium. During this period they were deprived of water and food and the urine and faeces excreted were collected to enable correction for the loss of ^{82}Br .

Half an hour before the animals were sacrificed the following recordings were started and performed in the order given: respiratory rate, roentgenographic examination of heart size and of lungs, heart rate, central venous pressure, mean arterial blood pressure and rectal temperature. Fifteen minutes before the animals were killed a standard amount of ^{125}I -albumin was injected intravenously to permit determination of the plasma volume.

Just before death of the animals blood samples were withdrawn for determination of electrolytes, radioactivity etc. For details see below.

Nephrectomised, non-overhydrated animals. 58 rabbits were used for investigation of the electrolyte-fluid distribution 12, 36, 60 and 84 hours after nephrectomy. The animals were deprived of food and water. The various subgroups are referred to as the 12, 36, 60 and 84 hr series.

In order to permit determination of the extracellular volume ^{82}Br and ^{51}Cr -EDTA were given *i.v.* 12 hours before the animals were killed and to estimate the plasma volume ^{125}I -albumin was administered *i.v.* 15 minutes before death, as in the controls.

Before the animals were sacrificed and at post-mortem they were examined and samples were obtained in the same way as in the control series.

Nephrectomised, overhydrated animals. In order to study the effect of iso- and hypo-osmotic overhydration on the electrolyte-fluid distribution, 78 nephrectomised rabbits were overhydrated to 5, 10, 15 and 20% of their bodyweight (BW_0) with 0.9% NaCl or 3% glucose solution, respectively. Overhydration was started immediately after nephrectomy and concluded within 2 hours. The animals were killed, 12 hours after nephrectomy.

To find out whether the effect of iso- and hypo-osmotic overhydration on the electrolyte-fluid distribution varied with the interval after nephrectomy, 48 animals that had been nephrectomised and deprived of water and food for 48 hours were overhydrated to 5, 10, 15 and 20% of their bodyweight (BW_{48}) with 0.9% NaCl or with 3% glucose solution. The animals were killed 12 hours after the beginning of overhydration, *i.e.* 60 hours after nephrectomy.

The series overhydrated with 0.9% saline and killed 12 hours after nephrectomy are hereinafter called the 12S-series (12 = killed 12 hours after nephrectomy, S = saline overhydration). In analogy herewith, the other three series are called the 12G, the 60S and the 60G-series (60 = killed 60 hours after nephrectomy, G = glucose overhydration). The 12 hr series and the 60 hr series served as controls.

^{82}Br , ^{51}Cr -EDTA and ^{125}I -albumin were given in the same way as to the nephrectomised non-overhydrated animals.

Before the animals were killed and at post-mortem the same examinations and samplings were performed as in the above mentioned series.

In order to minimise the risk of differences in the results between the various series because of seasonal variations etc. the animals in the various series were examined in a randomised sequence.

The material is summarised in the first table in the appendix.

EXPERIMENTAL TECHNIQUE

Nephrectomy. The retroperitoneal approach was used. Under local anaesthesia (2 ml Xylocain^R, 1%) an approximately three cm long incision was made in the lumbar region parallel to the median line and lateral to the long muscles of the back. The renal stalk was tied *en bloc* with double silk ligatures. Care was taken to keep the loss of blood at operation to a minimum.

In order to reduce the effect of the operative trauma on the results of the experiments the left kidney was removed ten days before the right. Only animals that appeared healthy after the leftsided nephrectomy and that increased in weight were accepted for further experiments.

Overhydration. Immediately after the injection of ⁸²Br and ⁵¹Cr-EDTA, i.e. 12 hours before the animals were sacrificed, infusion of sterile 0.9% NaCl or of 3% glucose solution was started in the 12S, 12G, 60S and 60G-series. The fluids were given via a catheter that had been inserted under local anaesthesia (1 ml Xylocain^R, 1%) into the right jugular vein. The rate of infusion was adjusted in such a way that the animals' bodyweight increased by 5% of BW₀ and BW₄₈, respectively, per half an hour. After the infusion the catheter was withdrawn.

Sacrifice. The animals were killed by a rapid injection of 1 ml of 4.5% enibomal sodium-solution (320 mOs/kg H₂O) per kg bodyweight via the catheter in the left jugular vein. The injection was immediately followed by apnoea, loss of consciousness and muscular hypotension. At thoracotomy (see below) the heart was invariably dilated and showed no visible activity.

PROCEDURES UNDERTAKEN AFTER SACRIFICE

Immediately after the animals had been killed the following measures were undertaken to keep the lungs aerated and to minimise redistribution of blood and fluid between the organs. After the trachea had been clamped the animals were thoracotomised and the large vessels of the heart, vena cava and the supradiaphragmatic part of the aorta were clamped. After laparotomy the portal vein, hepatic artery, aorta and vena cava below the liver were clamped. In the control series also the renal arteries and veins were

clamped. These measures were performed within 20–25 seconds of death of the animals. The free fluid in the abdominal and pleural cavities was removed, the volumes were measured and samples were taken for measurement of its radioactivity. In the control series the urinary bladder was emptied and rinsed with distilled water. The urine in the urinary bladder was weighed and subtracted from the total bodyweight (BW_A) and a sample of urine was taken for measurement of its ⁸²Br-activity.

Since a blood sample had been obtained from the inferior caval vein, the heart, lungs and trachea were removed *en bloc*. The pericardial sac was punctured and as much pericardial effusion as possible was aspirated and measured. When the volume of effusion was sufficient, it was kept for measurement of its radioactivity. The trachea was slit up and examined for any forthy fluid. After the lung surfaces had been examined the lungs were separated from the heart without loss of blood from the former. Vessels, fragments of bronchi, fat and lymph tissue were removed from the lung hili. The heart was freed from the parietal layer of the pericardium and the large vessels, and emptied of its blood. Visible residual blood in the heart was removed with a compress. The intestines, omentum and pancreas were removed *en bloc* (the intestinal preparation). The spleen was removed and freed from fat and vessels. In addition, the stomach with its contents and the liver together with the gallbladder were removed.

In the control series the kidneys were removed and freed from external vessels and fat.

The roof of the skull was opened and after the ventricular system had been emptied of its fluid the cerebrum was removed.

The eviscerated cadaver was skinned. The paws, ears, tail and subcutaneous fat were left attached to the skin, which was divided longitudinally into two equal parts.

The vastus lateralis (white skeletal muscle, WM) and the first head of the vastus intermedius (red skeletal muscle, RM) of the left quadriceps femoris were removed. Tendons, fascia and fat were dissected from the bellies of the muscles.

The residual cadaver which consisted mainly of the skeleton and the skeletal muscles, was pooled and was called the SM-preparation. The various preparations were placed immediately into weighed plastic vessels with a cap and weighed.

RECORDING METHODS AND ANALYSES

Half an hour before the animals were killed the following recordings and analysis were made.

The *respiratory rate* was recorded visually for two minutes. This was done before any other measures were taken that might irritate the animal.

The *general appearance and behaviour* of the animals were noted. Their reactivity as well as their muscle tone was judged as increased, normal or decreased, according to the behaviour of the animal and muscular resistance offered to the following measures to which they were subjected.

A *chest X-ray* was taken with the technique described by Lindqvist (1964). The roentgenographs were interpreted unaware of the group to which the animal belonged. Pulmonary changes, if any, were noted. The greatest roentgenographic length and breadth of the heart were measured. The greatest length $\times$ breadth of the heart in the roentgenograms in the control series was closely correlated with BW_0 ($r=0.85$, $p<0.005$). The quotient length $\times$ breadth (mm)/ BW_0 (kg) was therefore taken as a measure of roentgenographic size of the heart. This quotient is referred to in what follows as the *heart volume index (HVI)*.

The *bodyweight* was measured after the urinary bladder had been emptied (urethral catheterisation) after the removal of the second kidney (BW_0) (in the control series 12 hours before death), half an hour before sacrifice (BW_A) and in the 60S and 60G-series 48 hours after nephrectomy (BW_{48}).

The *heart rate* was recorded with a mingograph (Elema-Schönander, Stockholm).

The *rectal temperature* was measured with a thermometer with an accuracy of $\pm 0.1^\circ\text{C}$. The thermometer was inserted 3 cm into the rectum and read after 5 minutes. The same thermometer was used throughout the entire investigation.

Central venous pressure and blood pressure The animal was mounted in the supine position with the head immobilised on an operating table with a 3 cm deep, longitudinal groove in which the animal was placed. Under local anaesthesia (1 ml Xylocain^R, 1%) a polyethylene catheter filled with 0.9% saline, was inserted into the left jugular vein and fed up to a level 2 cm below the jugulum so that distinct oscillations reflecting the animal's respiration could be

observed in the level of the column of fluid in the catheter. To reduce the effect of the muscular tension over the chest on the central venous pressure the animal's front legs were loosened before recording the pressure. CVP is defined here as the height of the mean level of the oscillating surface of the fluid in the catheter above the level of the operating table, i.e. a point 3 cm ventrally to the back.

The left carotid artery was dissected free, care being taken to avoid injuring the vagus nerve. The artery was catheterised and the mean blood pressure (BP) was measured with a mercury manometer.

Blood sampling. Immediately after the end of overhydration a blood sample was withdrawn from an ear for measurement of the blood glucose concentration in the series overhydrated with 3% glucose solution. Fifteen minutes before the animals were sacrificed 1 ml of blood was obtained through the catheter in the carotid artery for measurement of Hb, hematocrit, blood glucose and acid base variables. Just before the animals were killed a further 10 ml of blood was obtained for measurement of the plasma electrolytes, plasma osmolality, plasma protein concentration, radioactivity in plasma and red blood cells as well as sodium and potassium concentrations in the red blood cells. At post-mortem examination 10 ml was obtained from the inferior caval vein for measuring the plasma creatinine and urea-N concentration. The last two samples were centrifuged and the plasma was separated off within 5 minutes. The plasma samples were afterwards stored at -20°C until examined.

Tissue sampling. After the various tissue preparations had been weighed at the autopsy the following tissue specimens were obtained.

A piece of the right lung base (about 0.5 g) was fixed in 5.7% formaldehyde solution for microscopic studies.

The lungs, the cerebrum and the kidneys (control series) were minced with scissors. The stomach was emptied of its content and the mucosa was rinsed quickly under running cold water. Signs of gastritis, if any, were noted, then the mucosa was dried with a compress and the empty stomach was weighed. The intestinal preparation, the stomach and the liver were homogenised. From the minced lung specimens, the minced brain tissue and the homogenised liver, aliquots of 1–2 g were taken for determination of their water and electrolyte content and for determination of their radioactivity.

Of the homogenised intestinal preparation, the homogenised stomach and the minced kidneys (control series) specimens of 2–3 g were taken for measurement of their water, fat and electrolyte content and radioactivity. One specimen of 1–2 g was also taken from the mixed gastric contents for determination of its radioactivity.

Pieces of 0.4–0.9 g from the left cardiac ventricle and from the bellies of the two quadriceps muscles were cut out for measurement of the water, fat and electrolyte content as well as radioactivity.

The spleen was left untouched and studied for radioactivity.

The samples that had been taken for determination of their water, fat and electrolyte content were placed in weighed 30 ml plastic beakers with caps and the samples intended for measurement of the radioactivity in the weighed 5 ml plastic tubes with caps. The specimens were weighed immediately on a balance with a precision of ± 0.1 mg (Sartorius analytical balance 2400).

All of the above measures had been performed within half an hour after the animals had been killed.

The SM-preparation was mixed with 50 ml redistilled water and boiled in a pressure cooker for 20 minutes. The boiled SM-preparation was afterwards passed through a mincing machine. The weight of the mixture was made up to the original weight of the preparation with redistilled water and homogenised. Double samples à 2–3 g of the homogenate were taken for determination of the water, fat and electrolyte content and radioactivity.

One half of the skin (alternating right and left) was set aside for determination of its water-, fat- and electrolyte content, while the other half was used for measuring its radioactivity.

CHEMICAL ANALYTIC METHODS

Blood and plasma. The *Hb* concentration was determined according to Drapkin and Austin (1935).

Haematocrit (hct) was determined with a micromethod. The buffy coat, which was never found to be more than 1 mm, was not included in the measurement of the column of the red blood cells. The samples were centrifuged for 20 minutes (11,500 r.p.m. $R = 8$ cm). The values obtained were multiplied by 0.98 to correct for the amount of trapped plasma.

The **blood glucose** concentration was determined according to Marks (1959).

The **acid-base balance** (*pH*, standard bicarbonate, base excess (*BE*) and *pCO*₂) was determined according to Siggaard-Andersen (1963), *pH* and *pCO*₂ were corrected for the difference between the temperature at which the blood samples were analysed (38°C) and the rectal temperature of the animal.

The **plasma sodium and potassium** concentrations were determined by flame photometry (Eppendorf). Propane was used as burning gas. The plasma samples were diluted with 5% trichloroacetic acid (TCA) and the precipitated proteins was removed by centrifugation. Three standard solutions corresponding to 100, 120 and 140 mEq/l were used for sodium analysis. The one with the concentration closest to that of a given sample was used. Also blank and standard solutions contained 5% TCA.

The **plasma calcium** concentration was determined by flamephotometry (Eppendorf). Ordinary standard methods were used, *i.e.* with acetylene as burning gas and addition of a detergent to the blanks and the standards. Three blank solutions containing a detergent and sodium corresponding to 100, 120 and 140 mEq/l were used in order to correct for the varying concentration of sodium in the plasma.

The **plasma chloride** concentration was determined with a potentiometric method (Aminco Cotlove automatic chloride titrator).

The **plasma magnesium** concentration was determined according to Natelson (1961).

The concentration of the **inorganic phosphorus** in plasma was determined according to Chen et al. (1956).

The **plasma protein** concentration was determined by the biuret method.

The **plasma osmolality** was analysed by freezing point depression.

The **plasma creatinine and urea-N** concentrations were determined by autoanalytical methods (Technicon, N-IIb and N-1c).

Tissues. The tissue specimens (except red blood cell concentrate and skin), whose water, fat and electrolyte content were to be determined were kept in the frozen state (-20°C) until the experimental procedures on the animals had been concluded, when all specimens of a given sort of tissue from all the animals were examined at the same time. The water content was calculated from the difference between the original weight of the specimen and its weight after it had been dried at 100–105°C for 12 hours. The dried intestinal

preparation, stomach, SM-preparation, heart muscle and skeletal muscle specimens were extracted with 25 ml redistilled petroleum ether (boiling point 30–60°C) for 24 hours, dried for 3 hours at 100–105°C, and weighed again. The fat content was calculated from the difference in weight of the specimen before and after extraction.

All specimens were extracted with 0.1 N nitric acid (1 ml/10 mg solids) for one month at room temperature. The samples were shaken once a week. The samples were weighed at the beginning and at the end of the extraction period, in order to enable correction of the results for evaporation during the extraction.

After its radioactivity had been measured the red blood cell concentrate was extracted with 5% TCA for 14 days without previous drying or fat extraction. The protein precipitate was spun down. The amount of water in the original red blood cell concentrate was calculated according to Eisenman et al. (1936, see under Formulas).

The amount of water in one half of the skin was determined by drying it at 100–105°C for 24 hours. The fat content was determined by extraction of the dry half of the skin with 500 ml diethyl ether 3 times and then drying the skin at 100–105°C for 3 hours. The half of the skin was then extracted for one month at room temperature with 500 ml 0.1 N nitric acid. As in the other tests, the results of the analysis were corrected for evaporation, if any, as calculated from the weight of the specimens at the beginning and at the end of the extraction period.

The sodium content and the potassium content of the extracts were measured by flame-photometry. The extracts were diluted with 0.1 N nitric acid (red blood cell concentrate with 5% TCA) so that they contained 0.1–0.4 mEq/l sodium and 0.1–0.5 mEq/l potassium, respectively. Sodium chloride and potassium chloride (0.1–0.5 mEq/l) dissolved in 0.1 N HNO₃ and 5% TCA were used as standard solutions. 0.1 N HNO₃ and 5% TCA, respectively, were used as blanks. The chloride content was determined potentiometrically (Aminco Cotlove automatic chloride titrator).

DETERMINATION OF PLASMA VOLUME AND EXTRACELLULAR WATER WITH THE ISOTOPE TECHNIQUE

The plasma volume was determined with the aid of ¹²⁵I-albumin and the extracellular volume was

determined with the aid of ⁸²Br and with ⁵¹Cr-EDTA (⁵¹Cr (III)-complex with ethylene diamine tetracetic acid).

The isotopes used were obtained from the Radiochemical Centre, Amersham, England. The code number of the ⁵¹Cr-EDTA-preparation used was CJ.13P, and those of ⁸²Br and ¹²⁵I BCP.3P and IMS.1P, respectively. The ⁸²Br-preparation was used for one week and that of ⁵¹Cr-EDTA for one month.

Preparation of ¹²⁵I-albumin. The globulins in fresh rabbit serum were precipitated by mixing serum and saturated ammonium sulphate solution in equal parts. The protein precipitate was removed by centrifugation and the supernatant was dialysed against re-distilled water to remove the ammonium sulphate. The solution obtained contained about 1% albumin.

20 ml of the albumin solution was mixed with 2 ml phosphate buffer (pH 7.15), 1 mCi carrier-free ¹²⁵I and 0.2 ml of 0.016% potassium chloride. During stirring of this mixture 0.2 ml of 0.25% sodium paratoluene sulphon-chloramide (chloramine T) was added 4 times at 0, 5, 10 and 30 minutes.

After the mixture had been stirred for a further 30 minutes it was placed in the refrigerator (+4°C) for 12 hours. The solution was then made isotonic and the content of free ¹²⁵I was reduced by dialysis against 0.9% saline. In order to eliminate denatured albumin and to reduce the content of free ¹²⁵I in the preparation still more, the latter was injected intravenously into a rabbit that was bled 12 hours after the injection. ACD (1/5) was added to the blood and the plasma was separated by centrifugation. The preparation obtained was diluted with fresh rabbit ACD-plasma and 0.9% saline so that the final solution contained about 1% protein and 1 ml had an activity of about 10⁷ c.p.m. The solution was stored in a refrigerator (±4°C) and used within at most one month. The amount of free ¹²⁵I determined after the proteins had been precipitated with TCA was less than 0.5% when the solution was fresh and less than 1.5% of the total ¹²⁵I after it had been stored for one month in the refrigerator.

Twelve hours before the animals were killed a catheter was inserted into the right jugular vein under local anaesthesia (1 ml Xylocain^R, 1%) and about 20 μCi NH₄ ⁸²Br and about 30 μCi ⁵¹Cr-EDTA each dissolved in 1 ml of 0.9% saline were injected in succession. In the control series the injections were followed by continuous infusion (4 ml/hr) of a 0.9% NaCl-solution containing about 1 mCi ⁵¹Cr-EDTA and 500 IU heparin per 100 ml.

1 ml of the ¹²⁵I-albumin solution prepared was injected via the catheter in the left jugular vein in 112 animals (see the first table in the appendix) 15 minutes before they were killed.

Approximately the same amounts of isotope stock solutions as given to the rabbits were diluted to 500 ml (^{82}Br and ^{51}Cr -EDTA) and 100 ml (^{125}I -albumin), respectively. These standard solutions were prepared in duplicates. The amounts of the stock solutions administered to the animals and standard solutions were determined gravimetrically to the nearest 0.1 mg. Rabbit serum was added to the ^{125}I -albumin standard solutions until they contained about 0.5% protein.

The radioactivity of the standard solutions (1 ml in duplicate), plasma (1 ml in duplicate), red blood cell concentrate (1 ml), ascitic fluid (1 ml), pleural effusion (1 ml), pericardial effusion (0.5 ml) and the various tissue specimens (regarding skin, see below) were measured in series on three occasions. The ^{82}Br -activity in the energy range of 400–900 KeV was measured on the day the animals were killed while the ^{51}Cr -activity in the energy range of 210–400 KeV and the total ^{51}Cr - and ^{125}I -activity in the energy range of 20–100 KeV were measured 3 weeks later, by which time the ^{82}Br -activity was negligible.

At least 10^4 counts were measured for each specimen and on each occasion. The activity recorded was corrected for background (measured in 1 ml water), the measuring geometry and the decay during the series of measurements. In the intervals between the measurements the specimens were stored in the refrigerator ($+4^\circ\text{C}$).

The ^{125}I -activity of the specimens was calculated, by subtracting the activity measured in the energy range of 20–100 KeV with the measured activity in the energy range of 210–400 KeV multiplied by the quotient between the activity in the energy range of 20–100 and 210–400 KeV found in the ^{51}Cr -EDTA-standard solutions.

Skin. The one half of the animal's skin was weighed and afterwards placed in a one liter plastic jar with a cap and 500 ml of 1 per cent benzethonium solution was added. 100 ml ^{82}Br , 100 ml ^{51}Cr -EDTA and 10 ml ^{125}I -albumin-standard solution were transferred to each of 3 other containers of the same shape and material and filled with water up to the same mark as that of the jar containing the skin and benzethonium.

Addition of extra protein to the latter jar did not affect the results. The isotope activity of the contents of the jars was measured over a plane crystal detector. The measurement were made according to the same time table and within the same range of energy as

that used for the other samples, but were started 3 days later. The background activity was measured in the same way but with a jar containing the same volume of water. At least 10^4 counts were measured for each sample on each occasion.

CONCENTRATION OF ELECTROLYTES AND ^{51}Cr -EDTA IN THE INTERSTITIAL FLUID

It was assumed here that the interstitial fluid contained only a negligible amount of protein. The sodium and potassium concentrations in the interstitial water were assumed to be the same as in plasma, as the correction factor for plasma water (p) and the Donnan factor (r) approximately counterbalance each other (Scribner & Burnell 1956, Bergström 1962). As for anionic chloride, bromide and Cr-EDTA, correction was made for both r and p, since in this case they both act in the same direction. As r-factor for chloride and bromide the theoretical Donnan factor for univalent ions 1.04, was used.

If EDTA be described as H_4Y , then Cr-EDTA at physiological pH will occur mainly as $\text{CrY}(\text{H}_2\text{O})^{1-}$ and as $\text{CrY}(\text{OH})^{2-}$. Since pK for the transformation between the univalent and the bivalent forms is 7.41 (see Lökken 1969) the concentration of the two forms should be roughly equal at physiological pH, and hence the total theoretical Donnan factor here would be about 1.06.

The following *in vitro* tests were carried out to check that the r-factors given above were of proper magnitude.

Five sealed cellophane bags filled with 5 ml of fresh rabbit serum to which had been added ^{82}Br and ^{51}Cr -EDTA, were dialysed for 24 hours at 38°C against 20 ml of 0.9% saline, buffered with a phosphate buffer to pH 7.3. The protein content, the chloride concentration, ^{82}Br - and ^{51}Cr -activity were afterwards measured in the inner and the outer fluid.

The mean protein concentration in the inner fluid was 5.9% (range 5.5–6.3), *i.e.* of the same magnitude as that of the plasma protein concentration in the experimental series, and in the outer fluid $<0.1\%$. The quotients between the outer and the inner fluid were on the average 1.081 for chloride (range 1.075–1.087), 1.080 for ^{82}Br (range 1.075–1.088) and 1.107 (range 1.094–1.112) for ^{51}Cr . The correction factor for the difference in amount of solids (protein)

between the two fluids was, according to Eisenman (1936), 0.96 ($1-0.00718 \times 5.9$) and accordingly the calculated r-factor for chloride was 1.035, for bromide 1.034 and for Cr-EDTA 1.06, *i.e.* of the same magnitude as the theoretical values.

As further evidence for the correctness of the r-factors it might be mentioned that the quotients between the activity of pericardial effusion and ascitic fluid, respectively, and plasma were 1.084 ± 0.008 and 1.054 ± 0.002 for ^{82}Br and 1.119 ± 0.010 and 1.090 ± 0.003 for ^{51}Cr . The protein content of the ascitic fluid was 1.3 ± 0.06 g/100 ml.

The r-factors were, of course, influenced by changes in pH and changes in the protein content and protein composition, but the magnitude of these errors was presumably small compared with that of the other sources of errors. This assumption is supported by the observation that no notable differences were found between the different experimental groups regarding the pertinent activity quotients between pericardial effusion and ascitic fluid on one hand and plasma, on the other.

RED BLOOD CELL CONCENTRATE

No significant difference was found between the distribution volume of ^{51}Cr -EDTA and that of ^{125}I -albumin in the red blood cell concentrates (mean 13.4 against mean 13.6 volume percent) in the 112 animals, where the plasma volume was measured with ^{125}I -albumin. The distribution volume of ^{51}Cr -EDTA was therefore used throughout as a measure of the plasma volume of the red blood cell concentrates in the calculation of $[\text{Na}]_{\text{rc}}$, $[\text{K}]_{\text{rc}}$ and $C_{\text{rc}}^{\text{Br}} / C_{\text{p}}^{\text{Br}}$. The mean distribution volume of ^{51}Cr -EDTA in the material as a whole was 13.2 volume percent (range 6.1–19.5).

MICROSCOPICAL STUDIES OF THE LUNGS

The piece of lung that was fixed in 5.7% formaldehyde solution was sectioned and stained with haematoxylin-eosin.

The microscopic lung changes were classed regarding the number of alveoli filled with protein precipitate, though oedematous fluid in the alveoli in the lungs, especially in acute pulmonary oedema is often

very poor in protein. Ten fields of vision (400 x) of lung tissue with roughly the same air content were examined and the lungs were classified according to the number of alveoles filled with protein precipitate in these ten fields of vision as (+) (1–2 alveoli filled with protein precipitate per 10 fields of vision), + (2–5), ++ (6–10) and +++ (>10).

The degree of interstitial oedema and cellularity of the alveolar septa were difficult to estimate because of hyperaemia of the preparation.

STATISTICAL METHODS

The data obtained were treated with conventional statistical methods such as t-test and linear regression analysis (Snedecor 1956, Kemp and Nielsen 1961, Rao 1962). The distribution of the values in the various series (C, 12 hrs . . . 12S5, 12S10 etc.) did not differ significantly from that of a Gaussian curve. In occasional uncertain cases the values were plotted on a normal distribution diagram.

In the regression equation $y = a + bx$, the letter y denoted the dependent variable (*e.g.* blood or tissue variable) and x the independent variable (in the nephrectomised, non-overhydrated series the number of days after nephrectomy and in the overhydrated series the degree of overhydration in percent). The b-value (the regression coefficient) thus denoted the mean change per day and per percent of overhydration, respectively and the a-value (the intercept) the y-value at time zero ("at nephrectomy") and without overhydration, respectively.

The values found in the control series were not included in the regression analysis of the values in the nephrectomised, non-overhydrated series. Whether the values found in the control series agreed with the values found at time zero ("at nephrectomy") of the nephrectomised, non-overhydrated series was judged partly from the trend in this series (by non-linearity) and partly by comparing the values in the control series with the a-value in the regression equation (by linearity). As previously mentioned, the 12 hr and 60 hr series were used as controls ($x = 0$) in the 12S and 12G respectively 60S and 60G series. When the curve for the values was convex upwards it was, for simplicity, called hyperbolic; when concave upwards, hypobolic.

The following levels of statistical significance were used: $p < 0.01$ significant, $0.01 < p < 0.05$ nearly or almost significant.

SYMBOLS

BV_B	Total blood volume (ml)
BW_0, BW_{48}, BW_A	Bodyweight (g) minus kidneys, with urinary bladder empty at beginning of experiment, 48 hours after nephrectomy and half an hour before sacrifice, respectively
C^{Br}, C^{Cr}, C^I	Count rate of ^{82}Br (400–900 KeV), ^{51}Cr (210–400 KeV) and ^{125}I (20–100 KeV), respectively
$C_A, C_p, C_{rc}, C_{rcp}, C_s$	Count rate per ml ascitic fluid, plasma, red blood cells, red blood cell concentrate and standard solution, respectively
C_{gc}, C_t	Count rate per g gastric content and wet tissue, respectively
C_{Rs}, C_{sS}	Count rate of the skin preparation and the skin standard, respectively
Cl	Total amount of chloride in organ (mEq)
D^{Br}, D^{Cr}, D^I	Administered amount (g) of ^{82}Br -, ^{51}Cr -EDTA- and ^{125}I -albumin stock solution, respectively
D_R, D_s	Administered amount (g) of isotope stock solution to rabbit and standard solution, respectively
$DV^{Br}, DV^{Cr}, DV^{Cl}$	Distribution volume (ml) of bromide, Cr-EDTA and chloride, respectively, in entire organ
DV_m	Distribution volume (ml) per 100 g solids
E	Symbol for sodium, potassium or chloride in the formula
E_m	mEq electrolytes per 100 g fat-free solids (brain)
E_i	Amount of intracellular electrolytes (mEq) per 100 g fat-free solids, calculated with Cr-EDTA as reference substance for extracellular fluid
$[E]_i, [E]_p, [E]_{rc}, [E]_{rcp}$	mEq electrolytes per liter intracellular fluid (calculated with Cr-EDTA as reference for extracellular fluid), plasma, red blood cells and red blood cell concentrate, respectively
$ECW^{Br}, ECW^{Cr}, ECW^{Cl}$	Amount of extracellular water (ml) calculated with ^{82}Br -, ^{51}Cr -EDTA and Cl respectively as reference
ECW_B	Total extracellular water in rabbit (ml)
F	Amount (g) of fat in organ
F_{cells}	The quotient between over all red blood cell percentage and arterial red blood percentage (hct). In this investigation a factor of 0.9 was used
FFS	Amount (g) of fat-free solids in organ
$\%FFS$	Percentage of fat-free solids in organ
H_2O	Amount (ml) of water in organ
$H_2O_e^{Br}, H_2O_e^{Cr}, H_2O_e^{Cl}$	Amount of extracellular water (ml) per 100 g fat-free solids determined with the aid of ^{82}Br , ^{51}Cr -EDTA and Cl , respectively, as references
$H_2O_i^{Cr}$	Amount of intracellular water (ml) per 100 g fat-free solids with use of Cr-EDTA as reference for the extracellular water
H_2O_m	Total amount of fluid (ml) per 100 g fat-free solids or solids (brain)
H_2O_{rc}	Amount of water (ml) in the red cell volume of the organ per 100 g fat-free solids
hct	Cell percentages of the central arterial blood, the haematocrit

ICW ^{Cr}	Volume (ml) of intracellular water calculated by means of ⁵¹ Cr-EDTA as reference substance for the extracellular water
ICW _B	Total amount of intracellular water (ml) in rabbit
K	Total amount of potassium (mEq) in organ
Na	Total amount of sodium (mEq) in organ
P	Correction factor for amount of solids in plasma (ml water per ml plasma)
PV	Plasma volume (ml) in organ
PV _B	Total plasma volume (ml) in animal
PV _m	Plasma volume (ml) per 100 g fat-free solids or solids (brain)
RCV	Red cell volume (ml) of organ
RCV _B	Total red cell volume (ml) in rabbit
RCV _m	Red cell volume (ml) per 100 g fat-free solids or solids (brain)
S	Amount of solids (g) in organ
%S	Percentage of solids in organ
TBCl, TBK, TBNa	Total body chloride, potassium and sodium, respectively (mEq)
TBF, TBS, TBW	Total body fat, solids and water respectively (g and ml respectively)
V _{FBF}	Amount of free body fluids (ascitic fluid - pleural effusion - pericardial effusion) (ml)
V _s ^{Br} , V _s ^{Cr} , V _s ^I	The volume (ml) of ⁸² Br-, ⁵¹ Cr-EDTA and ¹²⁵ I-albumin standard solution, respectively
W	Weight of organ (g)
W _{gc}	Weight of the gastric content (g)
W _{rc}	Water content of red blood cells (ml water per ml red blood cells)
W _{ST} , W _{Sis}	Total weight of rabbit's skin and weight of half the skin used for measurement of isotope activity (g)

Unless otherwise stated, BW₀ was used as reference for weights, amounts and volumes in the controls, the nephrectomised, non-overhydrated series, and the 12S and 12G series. BW₄₈ was in the same way used as reference in the 60S and 60G series. TBW, TBS and TBNa are as an example given in ml, g and mEq, respectively per kg BW₀ in the control series and in the 60S series in ml, g and mEq, respectively, per kg BW₄₈. As for the water no difference was made between g and ml.

FORMULAS

Plasma:

$p = 0.984 - 0.00718 \times \text{protein concentration (g/100 ml)}$; (Eisenman et al., 1936).

Red blood cells:

$w_{rc} = 0.9453 - 0.00704 \times \text{Hb} \times 100/\text{hct}$; (Eisenman et al., 1936).

$$\frac{C_{rc}^{Br}}{C_{rcp}^{Br}} = \frac{C_{rcp}^{Br} / C_p^{Br} - C_{rcp}^{Cr} / C_p^{Cr}}{1 - C_{rcp}^{Cr} / C_p^{Cr}};$$

$$[\text{Na}]_{\text{rc}} \text{ and } [\text{K}]_{\text{rc}} = \frac{[\text{E}]_{\text{rcp}} - C_{\text{rcp}}^{\text{Cr}} / C_{\text{p}}^{\text{Cr}} \times [\text{E}]_{\text{p}}}{1 - C_{\text{rcp}}^{\text{Cr}} / C_{\text{p}}^{\text{Cr}}};$$

$$[\text{Cl}]_{\text{rc}} = C_{\text{rc}}^{\text{Br}} / C_{\text{p}}^{\text{Br}} \times [\text{Cl}]_{\text{p}};$$

Total body:

TBW $\lesssim$ H₂O; (the blood specimens included, but not the gastric contents; the spleen was supposed to contain 70% water).

TBS $\lesssim$ FFS and S; (the blood specimens and the gastric contents not included).

TBF $= \lesssim$ F; (skin, SM-preparation, intestinal preparation, stomach and heart).

TBNa $= \lesssim$ Na; (the blood specimens included, but not the gastric contents and the spleen).

TBK $= \lesssim$ K; (see TBNa).

TBCl $= \lesssim$ Cl; (see TBNa).

$$\text{PV}_{\text{B}} = \frac{C_{\text{s}}^{\text{I}} \times D_{\text{R}}^{\text{I}} \times V_{\text{s}}^{\text{I}}}{C_{\text{p}}^{\text{I}} \times D_{\text{s}}^{\text{I}}};$$

$$\text{BV}_{\text{B}} = \frac{100 \times \text{PV}_{\text{B}}}{100 - \text{hct} \times F_{\text{cells}}}; \quad F_{\text{cells}} = 0.9$$

$$\text{RCV}_{\text{B}} = \text{BV}_{\text{B}} - \text{PV}_{\text{B}};$$

$$\text{ECW}_{\text{B}}^{\text{Cl}} = p / 1.04 \times \frac{1000 \times \text{TBCl} - [\text{Cl}]_{\text{p}} \times \text{PV}_{\text{B}} - [\text{Cl}]_{\text{rc}} \times \text{RCV}_{\text{B}}}{[\text{Cl}]_{\text{p}}} + p \times \text{PV}_{\text{B}};$$

$$\text{ECW}_{\text{B}}^{\text{Br}} = p / 1.04 \times \left[\frac{C_{\text{s}}^{\text{Br}} \times D_{\text{R}}^{\text{Br}} \times V_{\text{s}}^{\text{Br}}}{C_{\text{p}}^{\text{Br}} \times D_{\text{s}}^{\text{Br}}} - \text{PV}_{\text{B}} - C_{\text{rc}}^{\text{Br}} / C_{\text{p}}^{\text{Br}} \times \text{RCV}_{\text{B}} - \frac{W_{\text{gc}} \times C_{\text{gc}}^{\text{Br}}}{C_{\text{p}}^{\text{Br}}} \right] + p \times \text{PV}_{\text{B}};$$

$$\text{ECW}_{\text{B}}^{\text{Cr}} = p / 1.06 \times \left[\frac{C_{\text{s}}^{\text{Cr}} \times D_{\text{R}}^{\text{Cr}} \times V_{\text{s}}^{\text{Cr}}}{C_{\text{p}}^{\text{Cr}} \times D_{\text{s}}^{\text{Cr}}} - \text{PV}_{\text{B}} - \frac{W_{\text{gc}} \times C_{\text{gc}}^{\text{Cr}}}{C_{\text{p}}^{\text{Cr}}} \right] + p \times \text{PV}_{\text{B}};$$

$$\text{ICW}_{\text{B}}^{\text{Cr}} = \text{TBW} - \text{ECW}_{\text{B}}^{\text{Cr}};$$

In the controls the kidneys were not included in the calculation of the total body variables. Further the $\text{ECW}_{\text{B}}^{\text{Br}}$ in this series was corrected for the ^{82}Br loss via the urine and faeces. The $\text{ECW}_{\text{B}}^{\text{Cr}}$ was not calculated in the controls.

Skin:

$$PV = \frac{D_s^I \times C_{RS}^I \times PV_B \times W_{ST}}{10 \times D_R^I \times C_{sS}^I \times W_{Sis}};$$

$$BV = 100 \times PV / 100 - hct \times F_{cells}; \quad F_{cells} = 0.9$$

$$RCV = BV - PV;$$

$$ECW^{Cl} = p / 1.04 \times \frac{1000 \times Cl - [Cl]_p \times PV - [Cl]_{rc} \times RCV}{[Cl]_p} + p \times PV;$$

$$ECW^{Br} = p / 1.04 \times \left[\frac{V_s^{Br} \times C_{RS}^{Br} \times C_s^{Br} \times W_{ST}}{5 \times C_{sS}^{Br} \times C_p^{Br} \times W_{Sis}} - PV - C_{rc}^{Br} / C_p^{Br} \times RCV \right] + p \times PV;$$

$$ECW^{Cr} = p / 1.06 \times \left[\frac{V_s^{Cr} \times C_{RS}^{Cr} \times C_s^{Cr} \times W_{ST}}{5 \times C_{sS}^{Cr} \times C_p^{Cr} \times W_{Sis}} - PV \right] + p \times PV;$$

SM-preparation, white and red skeletal muscle and cardiac muscle:

$$PV_m = \frac{10^4 \times C_t^I}{\% FFS \times C_p^I};$$

$$RCV_m = \frac{100 \times PV_m}{100 - hct \times F_{cells}} - PV_m; \quad F_{cells} = 0.9$$

$$H_2O_{rc} = w_{rc} \times RCV_m;$$

$$H_2O^{Cl} = p / 1.04 \times \frac{1000 \times Cl_m - [Cl]_p \times PV_m - [Cl]_{rc} \times RCV_m}{[Cl]_p} + p \times PV_m;$$

$$H_2O_e^{Br} = p / 1.04 \times \left[\frac{10^4 \times C_t^{Br}}{\% FFS \times C_p^{Br}} - PV_m - C_{rc}^{Br} / C_p^{Br} \times RCV_m \right] + p \times PV_m;$$

$$H_2O_e^{Cr} = p / 1.06 \times \left[\frac{10^4 \times C_t^{Cr}}{\% FFS \times C_p^{Cr}} - PV_m \right] + p \times PV_m;$$

$$H_2O_i^{Cr} = H_2O_m - H_2O_e^{Cr} - H_2O_{rc};$$

$$Na_i \text{ and } K_i = E_m - \frac{[E]_p \times [H_2O_e^{Cr} + PV_m \times (1 - p)] + [E]_{rc} \times RCV_m}{1000};$$

$$Cl_i = Cl_m - \frac{1.04 / p \times [Cl]_p \times (H_2O_e^{Cr} - p \times PV_m) + [Cl]_p \times PV_m + [Cl]_{rc} \times RCV_m}{1000};$$

$$[E]_i = \frac{1000 \times E_i}{H_2O_i^{Cr}};$$

$$ECW = FFS \times H_2O_e / 100;$$

$$ICW^{Cr} = FFS \times H_2O_i^{Cr} / 100;$$

Intestinal preparation, stomach, gastric contents, liver, spleen, lungs and kidneys:

$$PV, DV^{Br} \text{ and } DV^{Cr} = W \times C_t / C_p;$$

$$DV^{Cl} = 1000 \times Cl / [Cl]_p;$$

Brain:

$$PV_m, DV_m^{Br} \text{ and } DV_m^{Cr} = \frac{10^4 \times C_t}{\%S \times C_p};$$

$$DV_m^{Cl} = 1000 \times Cl_m / [Cl]_p;$$

Free body fluids (FBF):

$$H_2O = V_{FBF} \times 0.984 - 0.00718 \times \text{protein concentration (g/100 ml)};$$

$$Na \text{ and } K = V_{FBF} \times [E]_p / 1000;$$

$$Cl = V_{FBF} \times C_A^{Br} / C_p^{Br} \times [Cl]_p / 1000;$$

The mean value of PV_B , PV and PV_m in the same experimental group were used in the formulas, when the values were not determined.

RESULTS AND COMMENTS

PRINCIPLES OF PRESENTATION OF THE RESULTS

C-12 hrs. The data given under this heading show the difference between the nephrectomised, non-overhydrated animals killed 12 hours after nephrectomy (the 12 hr-series) and the controls. This comparison was made to elucidate the initial effects of nephrectomy, which, as will be seen, often differed in magnitude and sign from those recorded later on after nephrectomy.

12-84 hrs. Data under this heading show the changes during the period 12-84 hrs after nephrectomy in the nephrectomised, non-overhydrated animals (the 12, 36, 60 and 84 hr-series).

12S and 60S and 12G and 60G. These series illustrate the effects of an increasing overhydration with 0.9% NaCl or 3% glucose solution on nephrectomised animals killed 12 hrs and 60 hrs, respectively, after nephrectomy. Comparisons were made between the 12S and 60S-series (S12-60 in the tables), 12G and 60G-series (G12-60), 12S and 12G-series (12S-G) and between 60S and 60G-series (60S-G).

Most of the numerical and the statistical results are given in tabular form (see Appendix) and in graphs. The numerical values given in the text denote the mean $\pm$ the standard error of the mean (SE).

GENERAL APPEARANCE AND BEHAVIOUR OF THE ANIMALS

C-12 hrs and 12-84 hrs. The behaviour and muscle tone of the nephrectomised, non-overhydrated animals appeared to be normal during the first 2 days after the operation. On the third day, however, they seemed to be listless except when handled for examination, when they offered considerable resistance. This combination of increased reactivity combined with depression is frequently seen in uraemic patients (see Schreiner & Maher 1961).

On the fourth day the animal became increasingly listless and tended to offer less resistance to examination. Four animals in the 84 hr-series died 72-84 hours after nephrectomy and were then excluded from the study.

12S and 60S and 12G and 60G. The overhydrated animals in the 60S-series reacted less strongly to different stimuli and offered less resistance to the examination than did the non-overhydrated animals in the 60 hr-series. Similar observations have been made by Lindqvist (1964) who reported that the appearance and the behaviour of highly uraemic rabbits were normalised after 15% overhydration with Ringer solution.

Overhydration with 3% glucose up to 10% of BW₀ and BW₄₈, respectively, had no notable effect on the general condition of the animals and their reactivity or muscular resistance at examination. When they were overhydrated to 15-20%, however, the muscles of the animals in the 12G-series as well as those in the 60G-series became hypotonic and the reactivity of the animals was reduced. Four animals which were overhydrated to 20% of BW₄₈ with 3% glucose had epileptiform convulsions and died immediately after the end of infusion and were therefore not included in the study.

These observations agree well with those made by other authors (see Lindqvist 1964). The changes in the appearance and behaviour of the animals overhydrated with glucose solution were probably due mainly to cerebral oedema (see below).

MEAN ARTERIAL BLOOD PRESSURE (BP), CENTRAL VENOUS PRESSURE (CVP), HEART RATE AND HEART VOLUME INDEX (HVI) (Fig. 1)

C-12 hrs. The BP was nearly significantly, the CVP significantly, and the heart rate numerically, higher in the 12hr-series than in the controls. The HVI was nearly significantly less in the 12 hr-series than in the controls.

12-84 hrs. The curve for the BP continued to rise hyperbolically during the period 12-84 hours after nephrectomy from 106 ± 2.5 to 120 ± 3.7 mm Hg. The other variables did not change significantly during this period.

12S and 60S and 12G and 60G. Overhydration had no clear effect on the heart rate and the BP. On the other hand, the HVI and the CVP invariably increased. As is apparent from Fig. 1, the curve for the CVP was hyperbolic in the two NaCl-overhydrated series as was that of the HVI in the 60S and 60G-series. No notable differences were found between the four series in respect of the magnitude of the increase in HVI and in CVP.

In the evaluation of the heart volume index, it should be borne in mind that the examination was carried out with the animal suspended with its head uppermost and that the sagittal diameter of the heart was not measured. The heart rate, the CVP and the BP were measured while the animal was under stressing conditions and lying on its back, which may have influenced the values recorded. The values obtained must therefore be judged with caution.

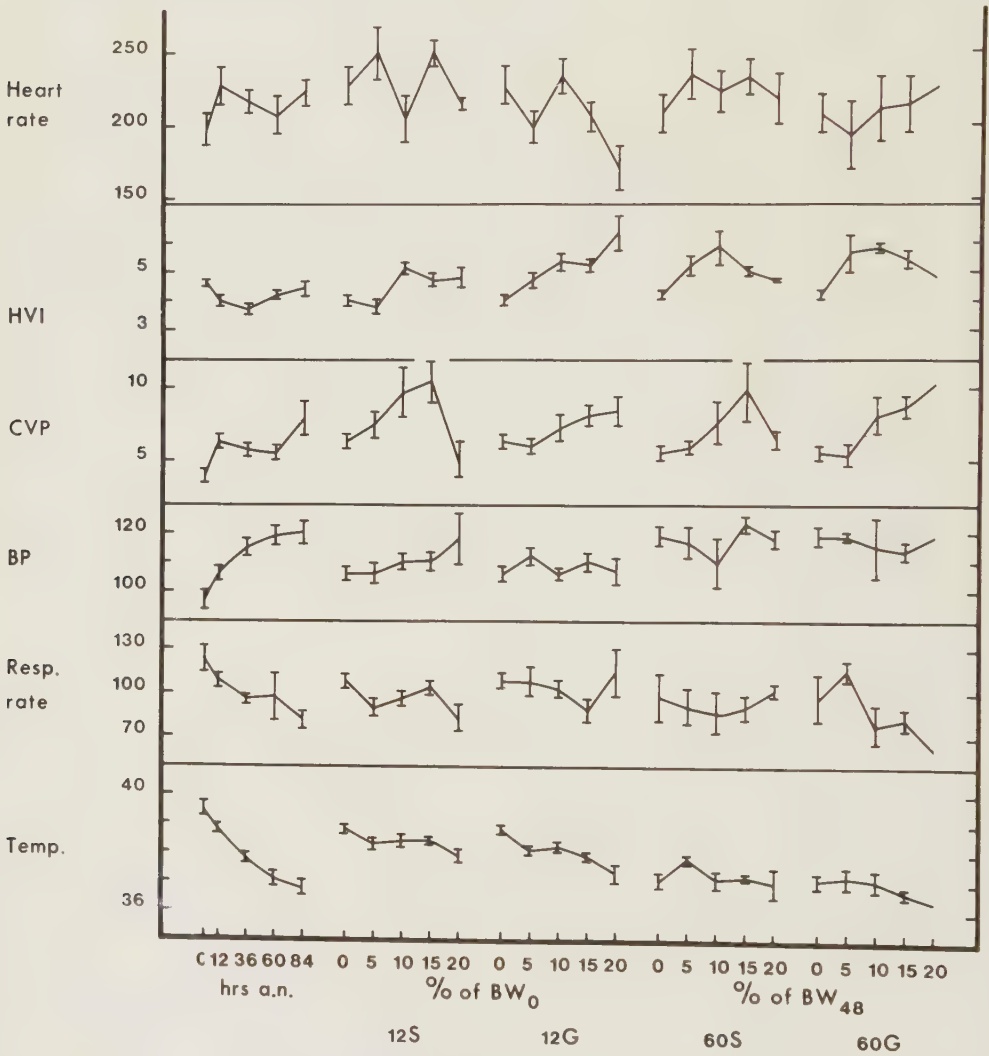


FIG. 1. Effect of nephrectomy and nephrectomy plus overhydration on some circulatory variables, the respiratory rate and the rectal temperature. The verticals denote $\pm$ standard error of mean (SE). The first curves from the left (hrs a.n.) denote the course with time after nephrectomy: the following curves, changes in the 12S, the 12G, the 60S and the 60G series with degree of overhydration.

A notable finding was that the BP increased in the rabbits in the present study after nephrectomy. Renoprival hypertension has previously been denied in rabbits (Giordano et al. 1960). Pickering (1945) recorded even a reduction of the blood pressure in the rabbit after nephrectomy.

There are two main hypotheses of the development of renoprival hypertension in experimental animals. One of these ascribes the hypertension to changes in electrolyte-fluid distribution, while the other claims it to be of hormonal origin. The latter hypothesis has recently been strengthened by the discovery that the kidney contains substances (inter alia prostaglandins) with vasodepressor and antihypertensive activity (see Page and McCubbin 1969, Wilson et al. 1971).

The observations made in the present study do not support the view that electrolyte-fluid disturbances cause the renoprival hypertension, at least not in the rabbit, since the marked changes in electrolyte-fluid distribution in the overhydrated animals did not notably influence the blood pressure.

It is not known whether the recorded renoprival hypertension in the present study should be ascribed to an increased cardiac output or to an increased peripheral resistance or to both. An increased cardiac output initially after nephrectomy may be presumed because the blood volume, the CVP and the heart rate were then increased. During the 12–84 hr period after nephrectomy the CVP persisted at a relatively high level which may have maintained an increased cardiac output also during this phase. Ledingham (1960, 1961) observed that the cardiac output was increased in heart-lung preparations from rats three days after nephrectomy in comparison with those from normal rats at the same atrial filling pressure. He ascribed this to the hyperpotassaemia of the uraemic preparations. An increased cardiac output in renoprival hypertension has been reported to occur in the dog by Krieger & Hamilton (1958) and in the rat by Ledingham & Pelling (1970).

It should be noted that glucose overhydration did not cause any increase in the blood pressure in spite of the fact that the body fluids in the animals were markedly hypo-osmolar. There is much experimental evidence that infusions of hypo-osmolaric solutions increase the local peripheral resistance (see Jonsson 1970). In addition, the animals in these series developed cerebral oedema which normally raises the blood pressure.

RECTAL TEMPERATURE (Fig. 1)

C-12 hrs and 12–84 hrs. The rectal temperature was nearly significantly lower in the 12 hr-series than in the control series.

The rectal temperature fell considerably during the period 12–84 hrs after nephrectomy with about 0.7°C per 24 hrs (from 38.8 ± 0.16 to $36.8 \pm 0.25^{\circ}\text{C}$). The initial fall of the rectal temperature (C-12 hrs) did not differ from this rate of decrease. As is apparent from the figure, the rate of decrease appears to diminish somewhat with the interval after nephrectomy.

12S and 60S. The rectal temperature fell almost significantly in the 12S-series. In the 60S-series, on the other hand, no significant change in rectal temperature was recorded.

12G and 60G. The rectal temperature fell in the 12G-series. In the 60G series, on the other hand, as in 60S-series no significant change in the rectal temperature was noted. The fall in temperature in the 12G-series was numerically twice as large as in the 12S-series.

That uraemia is associated with hypothermia is an old observation (Bradford 1892). It is also well known that the depression of the body temperature is correlated to the height of azotemia (compare the hypobolic decrease in the rectal temperature and the hyperbolic increase in the plasma creatinine and urea concentration after nephrectomy in the present study). This together with the fact that hypothermia develops in animals after injections of urine, extracts of uraemic plasma and spinal fluid or urea (see Schreiner & Maher 1961) suggests that the hypothermia is caused mainly by one or more uraemic substances. Freeman (1971) found that the uraemic hypothermia 12 hrs after bilateral ureteral ligation in rats could be accentuated by hypermagnesaemia. In the present study there was, however, no correlation between the plasma Mg concentration and the rectal temperature in the 12 hr-series, nor was any obvious correlation found between these two variables in the rest of the study. That the rectal temperature fell in the 12S and 12G-series in the present study, however, suggests that other electrolyte-fluid factors may contribute to the uraemic hypothermia. Why the rectal temperature fell in the 12S and 12G-series but not in the 60S and 60G-series in the present study is difficult to explain. The animals in the last mentioned series, however, had a marked hypothermia before overhydration and it is therefore likely that a

further reduction of the temperature was counteracted by stronger regulatory mechanisms than in the 12S and 12G-series.

RESPIRATION (Fig. 1)

C-12 hrs and 12-84 hrs. The respiratory rate was numerically somewhat lower in the 12 hr-series than in the controls.

The respiratory rate fell during the 12-84 hr period after nephrectomy from 108 ± 5 to 81 ± 6 per minute at the same time as the respiration became deeper and more regular.

12S and 60S and 12G and 60G. Overhydration had no clear effect on the respiration pattern.

None of the animals showed evidence of dyspnoea or overt signs of pulmonary oedema.

In spite of the fact that alveolar ventilation increased, i.e. pCO_2 decreased as compensation for the increasing metabolic acidosis after nephrectomy, the

respiratory rate decreased. Obviously the tidal volume increased. A decreasing respiratory rate was also recorded by Lindqvist (1964) after bilateral ureteric ligation in rabbits.

That no dyspnoea or apparent signs of pulmonary oedema and no conclusive change of the respiratory rate were observed in the overhydrated series, suggests that the overhydration in the present study did not cause pulmonary oedema of importance.

PLASMA OSMOLALITY, PLASMA CREATININE AND PLASMA UREA-N (Fig. 2)

C-12 hrs. The plasma creatinine and urea-N concentrations were higher in the 12 hr-series than in the controls. The plasma osmolality, on the other hand, was the same in both series.

One might have expected plasma osmolality to be somewhat higher in the 12 hr-series than in the control

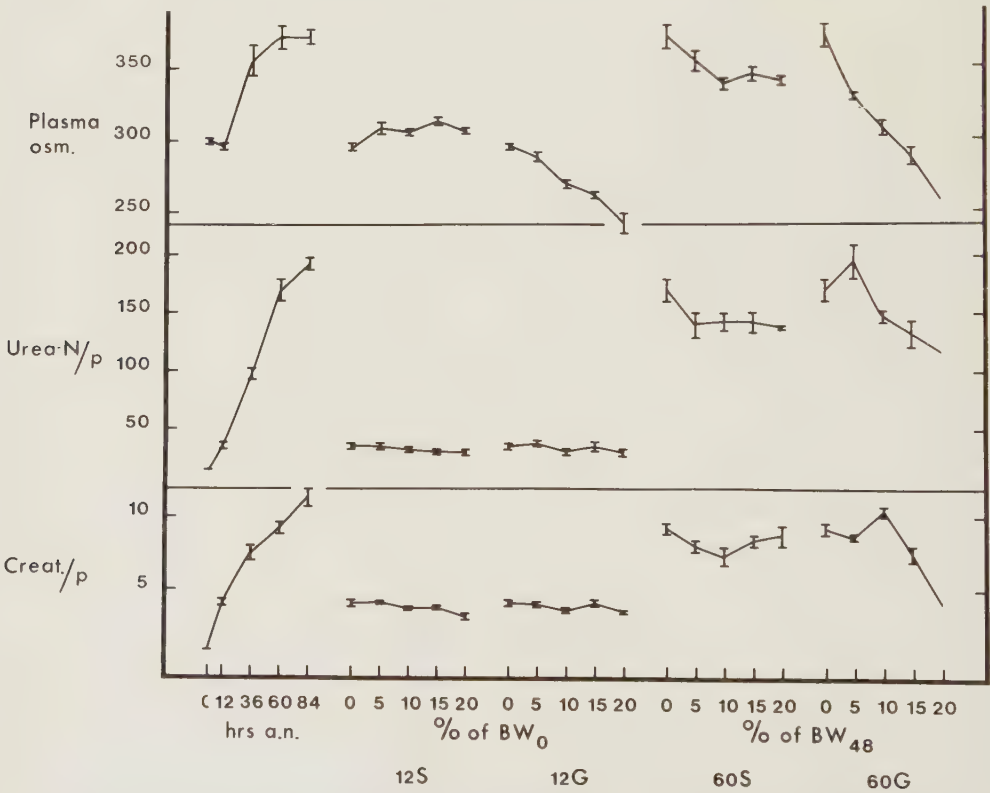


FIG. 2. Effect of nephrectomy and nephrectomy plus overhydration on the plasma osmolality (mOsm/kg H₂O), the plasma urea-N (mg/100 ml) and creatinine concentration (mg/100 ml). For further explanation, see fig. 1.

series because the plasma K, Ca and Mg concentrations were raised in this series as well as the plasma creatinine and urea-N concentrations. Lack of parallelism is, however, often found between the calculated osmolality and the observed osmolality in uraemia (Maher and Schreiner 1961).

12–84 hrs. The plasma osmolality increased during the 12–84 hr period after nephrectomy along a markedly hyperbolic curve. The plasma creatinine and plasma urea-N concentrations increased during this time from 4.1 ± 0.2 and 34 ± 2.5 mg/100 ml, respectively, to 11.3 ± 0.6 and 192 ± 5 mg/100 ml. It is also clear from the figure that the plasma creatinine and urea-N concentrations rose along hyperbolic curves. The calculated osmolality did not agree completely with determined osmolality (see above). That the azotemia increases hyperbolically in acute uraemia has also been observed by other workers (see Maher and Schreiner 1961, Lindqvist 1964). In the present study the deprival of food might have contributed to this phenomenon.

12S and 60S and 12G and 60G. The plasma osmolality increased slightly in the 12S-series and fell markedly, as expected, in the other three series. The plasma urea-N and creatinine concentrations fell (although not significantly in all the series) to values differing but little from those expected as the distribution volume of these two substances are largely the same as the total body water (McCance & Widdowson 1951, Edwards 1959, Schloerb 1960). That the plasma osmolality increased in the 12S-series was probably because the osmolality of the infused NaCl-solution was somewhat higher than that of the extracellular fluid.

PLASMA PROTEIN CONCENTRATION AND CALCULATED INTRAVASCULAR AMOUNT OF PROTEINS (Fig. 3)

C-12 hrs and 12–84 hrs. There was no difference in plasma protein concentration between the controls and the 12hr-series, but the intravascular amount of proteins was considerably larger 12 hrs after nephrectomy than in the controls, mean 3.2 g and 2.4 g per kg BW₀, respectively.

The plasma protein concentration increased during the 12–36 hr period after nephrectomy and afterwards persisted at a relatively high level. The intravascular amount of proteins, on the other hand,

remained largely unchanged throughout the 12–84 hr period after nephrectomy.

The initial increase in the intravascular amount of proteins can hardly be ascribed to the operation trauma *per se* since such a trauma has, if anything, the opposite effect on the intravascular amount of proteins. An increased plasma protein concentration after nephrectomy has been noted earlier (see Schreiner & Maher 1961). This phenomenon has been ascribed to, among other things, dehydration. But this was not the case in the present study. The TBW and TBNa increased numerically and the extracellular volume appeared to increase initially after nephrectomy. Parallels may therefore possibly be drawn between the initial increase of the intravascular amount of proteins and the increase occurring on infusion of large amounts of saline solution (Stewart & Rourke 1941, Harroun et al. 1950, Keating et al. 1953). The increase in the intravascular proteins under such conditions might be explained by a shift of proteins from the interstitial to the intravascular space because of an increased lymph flow (Guyton 1965, Guyton & Coleman 1968).

That the plasma protein concentration increased later after nephrectomy in the present study might be ascribed mainly to a certain concomitant reduction of the plasma volume.

Some change in the plasma protein composition may, of course, have contributed to the values found.

12S and 60S and 12G and 60G. The plasma protein concentration decreased in all four overhydrated series. The decrease was numerically somewhat larger in the 60S and 60G-series. On the other hand, no notable difference was found between the 12S and 12G-series or between the 60S and 60G-series. Judging from the figures, the curves for the decreases in all four series were not linear but hypobolic. In all four series the intravascular amount of proteins decreased after a small initial increase. In the 12S-series and 12G-series it decreased from a mean of 3.2 g to 2.6 g and 2.8 g per kg BW₀, respectively, and in the 60S and 60G-series, from a mean of 3.4 g to 2.8 and 2.9 g per kg BW₄₈, respectively. The plasma volume increased hyperbolically (Fig. 18) with increasing degree of overhydration, and at 20% overhydration the values were lower or equal to the original values.

The changes in the plasma protein concentration were thus the result of changes both in the plasma volume and in the intravascular amount of proteins.

The initial small increase in the intravascular amount of protein may correspond to the increase that has been noticed by other authors after infusion of large amount of fluids (see above).

The decrease in the intravascular amount of proteins on heavier overhydration might have been due to the marked extension of the interstitial space with consequent dilution of the proteins in that space. Such dilution presumably caused a net shift of proteins from the intravascular to the extravascular compartment. That changes in capillary permeability to proteins might have contributed to the results obtained cannot be excluded.

BLOOD GLUCOSE (Fig. 3)

C-12 hrs and 12-84 hrs. The blood glucose concentration tended to rise somewhat after nephrectomy. It is a commonplace that uraemia is associated with disturbances of the glucose metabolism including, among other things, an increased fasting blood glucose concentration and reduced glucose tolerance (see Bergström & Bittar 1969). It was because of these disturbances and because the extracellular glucose concentration affects the fluid distribution, that the blood glucose concentration was determined in the present investigation.

Since the concentration of glucose is lower in the erythrocytes than in plasma in the rabbit (see Troschin 1966), parallel changes in the haematocrit must be taken into account in the evaluation of changes in the blood glucose level.

The advancing uraemia did not cause an increase in the blood glucose despite decreasing glucose tolerance, as demonstrated by the fact that the blood glucose level was clearly higher in the 60G than in the 12G-series after the glucose infusion (see below). The slight tendency of the blood glucose concentration to rise after nephrectomy can hardly have had more than a negligible effect on the fluid distribution.

12S and 60S and 12G and 60G. The blood glucose level fell significantly and nearly significantly, respectively, in the 12S and 60S-series. The decrease leveled off at 10% overhydration. In the 12G series the blood glucose concentration persisted at the same level as in the 12hr-series. In the 60G series the blood glucose concentration rose nearly significantly.

The non-linear fall of the blood glucose levels in the two series overhydrated with saline can probably be explained by dilution, and at 15-20% overhydra-

tion, by secondary regulatory mechanisms. The magnitude of the extracellular amount of glucose at 15-20% overhydration must, however, have been small from the point of view of fluid distribution (< 1 mmol per kg BW_0 and BW_{48} , respectively).

In the 12G-series the blood glucose level had become normal after the glucose infusion. In the 60G-series, however, this was not the case, evidently because of reduced glucose tolerance. In both series the extracellular amount of glucose increased with the degree of overhydration. This might have helped to bind water to the extracellular space, but the magnitude of this increase must have been relatively small from a point of view of fluid distribution (max. 1 and 2 mmol/kg BW_0 and BW_{48} , respectively).

The mean blood glucose levels immediately after overhydration were: 268 ± 44 , 314 ± 15 , 388 ± 29 and 444 ± 2 mg/100 ml, respectively in the 12G5, 12G10, 12G15 and 12G20-series. The corresponding values in the 60G-series were: 353 ± 48 , 361 ± 15 , 481 ± 49 and 597 mg/100 ml, respectively, i.e. about 100 mg/100 ml higher than in the 12G-series. In the four animals that died very soon after the end of the infusion of glucose solution the blood glucose concentration was 510-768 mg/100 ml. The highest values noted in the 12G and 60G-series were 615 and 871 mg/100 ml, respectively.

HAEMOGLOBIN CONCENTRATION (Hb), HAEMATOCRIT (hct) AND CALCULATED RED CELL VOLUME (RCV_B) (Figs. 3 and 18)

C-12 hrs and 12-84 hrs. Autopsy revealed no signs of haemorrhage, apart from occasional small, red spots on the lung surfaces. The Hb and the hct tended to increase initially after nephrectomy, but afterwards returned to the level in the control series. The mean red cell Hb concentration was 29.0, 27.5, 31.0 and 28.1% in the 12, 36, 60 and 84 hr-series, respectively. The calculated red cell volume first increased from 20.8 ± 0.4 to 25.9 ± 1.5 ml/kg BW_0 , after which it successively decreased, and by 84 hrs after nephrectomy it had reached the level found in the control series.

At determination of the haematocrit no attempts were made to determine the amount of trapped plasma. The hematocrit was used mainly for calculating the blood volume from the determined plasma volume, and in the present investigation the variation of the

relative amount of the plasma among the red cells was presumably small compared with the uncertainty of the F_{cell} -factor used. As a plasma trapping factor use was instead made of a constant value of 0.98, a value obtained from published experiments in which

the measuring conditions corresponded to those in the present study (see Chien & Gregersen 1962). A value of 0.90 was used as F_{cell} -factor, which was that found by Zizza & Reeve (1958) in rabbits in which the plasma volume had been determined with ^{131}I -

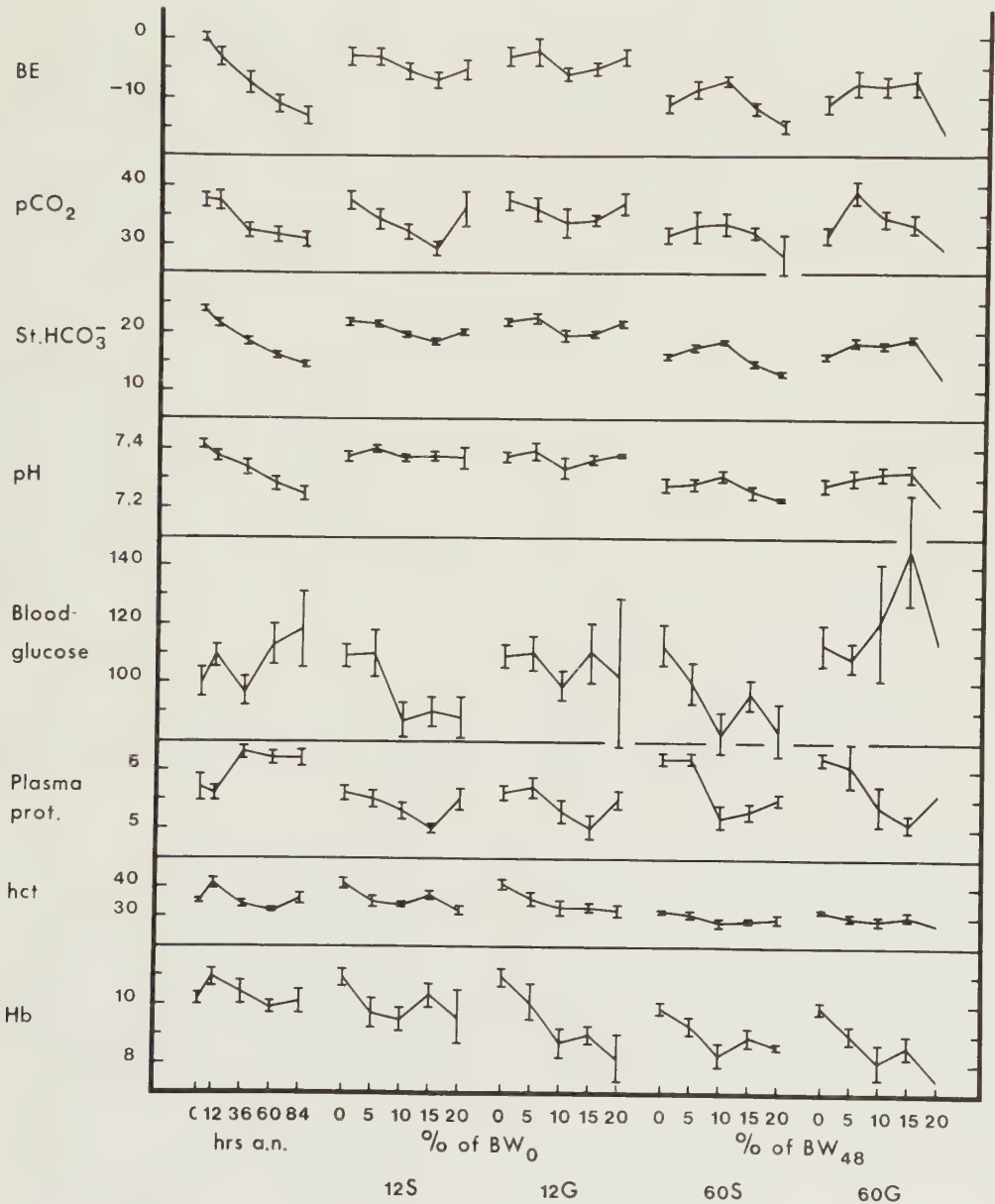


FIG. 3. Effect of nephrectomy and nephrectomy plus overhydration on the acid base balance, the blood glucose concentration (mg/100 ml), the plasma protein concentration (g/100 ml), the hematocrit and the hemoglobin concentration (g/100 ml). For further explanation, see fig. 1.

albumin and the red cell volume with ^{32}P -labelled erythrocytes. Though much suggests that the F_{cell} -factor varies but little with the experimental conditions used (see Gregersen et al. 1953), it cannot be excluded that the factor might have changed somewhat under the present experimental conditions, though not to such an extent as to exclude its acceptability for the purpose in view.

Nephrectomy is generally sooner or later followed by anaemia. It is ascribed partly to depression of the bone marrow owing to decreased production of erythropoietin and presumably also a primary uraemic toxic effect on erythropoiesis, and partly to increased red cell destruction owing to disturbed erythrocyte metabolism (see Schreiner & Maher 1962, Bergström & Bittar 1969, Erslev 1970, Wills 1971).

In rabbits allowed water and food *ad lib* Muirhead et al. (1952) found the following haematologic changes, compared with the values in sham-operated controls three days after nephrectomy: a reduction of Hb (9.4 in the nephrectomised animals against 12.2 g/100 ml in the controls), hct (28.6% against 32.1%), red cell volume (19 against 31 ml per kg BW), and reticulocyte count, and an increased serum Fe and TIBC, iron in liver and spleen, serum bilirubin and faecal excretion of urobilinogen and mechanical fragility of the erythrocytes. The anaemia in the nephrectomised animals was normochromic and normocytic. The microscopical picture of the bone marrow was normal or contained an increased percentage of normoblasts. The authors concluded that nephrectomy is soon followed by anaemia of mainly haemolytic type in the rabbit.

The reason why anaemia did not develop after nephrectomy in the present investigation was presumably that red cells were liberated from their stores initially after nephrectomy, and perhaps that the animals were deprived of water and food after nephrectomy. In the study of Muirhead et al. (1952) the free access to water might have resulted in a reduction of the extracellular effective osmolality and thereby in an increased haemolysis (compare glucose overhydration, below). The free access to food may also have resulted in a higher tissue fluid concentration of substances toxic to the erythrocytes and the erythropoiesis (see Erslev 1970). That the water and food intake may play some role in this connection is supported to some extent by Ledingham & Pelling's (1970) observation that no change occurred in the red cell volume in

nephrectomised rats allowed a certain ration of water and saline and deprived of food for the first three days after nephrectomy. Erslev (1960) found that the red cell production was decreased in nephrectomised rabbits. This reduction was found to be an effect of azotaemia rather than lack of renal tissue.

12S and 60S. The haematocrit fell nearly significantly in the 12S-series, and the Hb fell significantly in the 60S-series. It is clear from the figure that also Hb in the 12S-series and the hct in the 60S-series tended to fall. The red cell Hb concentration showed a tendency to rise somewhat in the 12S-series and to fall in the 60S-series (from on the average 27.5% to 29.9% and from 30.8% to 29.2% respectively). The calculated red cell volume did not change significantly in any of the series.

12G and 60G. Hb fell in both the 12G and 60G-series, while hct decreased significantly in the 12G-series and nearly significantly in the 60G-series. As might be expected, the red cell Hb concentration in both series fell (from on the average 27.5 g/100 ml to 26.6 g/100 ml in the 12G-series and from 30.8 to 27.1 in the 60G-series). The calculated RCV_B did not change significantly in either of the two series. The calculated intravascular amount of Hb decreased in both series by about 30% (about 2 g/kg BW_0 and BW_{48} , respectively).

Overhydration with glucose caused osmotic haemolysis in both series. One might have expected this to be more pronounced in the 60G-series than in the 12G-series since the erythrocyte fragility is increased in uraemia (Muirhead et al. 1952, Schreiner & Maher 1961).

ACID BASE STATUS (Fig. 3)

C-12 hr and 12-84 hr. The animals got an increasing metabolic acidosis after nephrectomy, partly compensated by a decreasing pCO_2 . The pH, pCO_2 , standard bicarbonate and base excess fell by, on the average 0.04 unit, 2.2 mm Hg, 2.4 mEq/l and 3.3 mEq/l, respectively, per 24 hrs during the period 12-84 hrs after nephrectomy. The rate of change seemed to be the same during the first 12 hrs after nephrectomy.

12S and 60S and 12G and 60G. The pCO_2 decreased significantly and the base excess nearly significantly in the 12S-series. Otherwise no clear changes of the acid balance variables could be observed in the over-

hydrated series. Thus no significant dilution acidosis was observed at the sacrifice of the animals.

PLASMA SODIUM, POTASSIUM AND CHLORIDE (Fig. 4)

C-12 hrs and 12-84 hrs. The plasma K concentration was higher, and the plasma Cl concentration lower, in the 12 hr-series than in the controls. The plasma Na concentration was the same in both series.

From 12 to 60 hrs after nephrectomy the plasma K concentration continued to rise at the same rate as during the first 12 hours; it rose from 5.3 ± 0.2 to 8.6 ± 0.4 mEq/l, after which it fell to 7.5 ± 0.4 mEq/l 84 hrs after nephrectomy. During the 12-36 hr period the plasma Na concentration fell from 144 ± 0.9 to 136 ± 2.7 mEq/l and afterwards persisted at this relatively low level. The plasma Cl concentration fell almost significantly at the rate of about 1.2 mEq/l per 24 hrs throughout.

The rate of increase of the plasma K concentration during the period 12-60 hrs after nephrectomy was of the same magnitude as that found by Lindquist (1964) in rabbits after bilateral ureteric ligation for a corresponding period. In his investigation, in which the animals were allowed to eat *ad lib* the plasma K concentration continued to increase also after this period, which it apparently did not in the present study.

The plasma K concentration after nephrectomy varies with, among other things, the exogenous supply of K, the extra-renal loss of K (faecal loss) the maintenance of the cell gradient for K (the Na-K pump and the intracellular K-binding capacity), the ratio between catabolism and anabolism, disintegration of cells (inter alia haemolysis) the degree of hydration and the extracellular volume (Scribner & Burnell 1956). That the plasma K concentration tended to fall in the late stage after nephrectomy in the present study may be regarded as a consequence of the fact that the faecal loss of K exceeded the factors that caused the plasma K concentration to increase.

A decreased plasma Na concentration in experimental acute renal failure has been reported by, among others, Hamburger (1954, 1957), Rush & Randall (1957), Aach et al. (1957).

The plasma sodium concentration after bilateral nephrectomy varies with, among other things, the enteric load and absorption of Na, the extrarenal loss

of Na (faecal loss), the degree of hydration, the concentration of other substances capable of influencing the effective osmotic pressure of the extracellular fluid and thereby the extracellular volume, the capacity of extracellular structures to bind sodium (especially the skeleton) and the capacity of the Na-K pump. Since the exogenous supply of water and Na is of importance, the results will depend largely on the experimental conditions in this respect, which is also apparent from the results in the overhydrated series. In the present study, in which the animals were deprived of water and food after nephrectomy, the plasma Na concentration fell. As will later be apparent, this reduction could be ascribed to a shift of Na from the extra to the intracellular compartment and probably also to an increase in the extracellular volume. The relative reduction of TBW and that of TBNa were equal. Hence, the loss of sodium did not contribute to the fall in the concentration of the plasma Na.

That the plasma Cl concentration falls in acute renal failure and in experimental acute uraemia is well known. In the present study the decrease of the plasma Cl concentration was not due to a decrease of the TBCl and must be ascribed to a shift of Cl from the extra to the intracellular volume, which was observed in white and red skeletal muscle, for example, and probably also to a dilution because of an increase in the extracellular volume. The decrease of the plasma Cl concentration should, of course, be related to the increase of the plasma phosphate and sulphate concentrations following nephrectomy.

12S and 60S. In the 12S-series the plasma Cl concentration rose considerably, while the plasma Na concentration increased somewhat numerically, and the plasma K concentration persisted unchanged. In the 60S-series the plasma Na and Cl concentration rose from 136 ± 1.7 to 146 ± 1.9 and from 96 ± 1.0 to 117 ± 0.6 mEq/l, respectively, while the plasma K concentration decreased.

The fact that the plasma K concentration did not fall in the 12S-series implies that the extracellular amount of K increased in this series (see Total body). This addition of K may have been derived mainly from the intracellular space of the skeletal muscles, since the intracellular amount of K decreased in both the white and red skeletal muscle in this series.

In the 60S-series the plasma K concentration fell in proportion to the extension of the extracellular space. In other words, the extracellular amount of K seemed

not to change in this series. Nevertheless, also in the 60S-series there occurred a significant loss of intracellular K in the skeletal muscles of the same magnitude as in the 12S-series. This means that there might have occurred a re-distribution of K from muscle cells to other intracellular compartments in the 60S-series.

The observed increase of the plasma Na and Cl concentrations in the two saline overhydrated series was due to the fact that the infused solution had higher concentrations of these two ions than the extracellular

fluid in the nephrectomised, non-overhydrated rabbits.

12G and 60G. The plasma K concentration did not change in the 12G-series, which means that the extracellular amount of K increased. The plasma Na and Cl concentration fell, but not proportionally to the extension of the ECW_{B}^{Cr} . The extracellular amount of Na and Cl thus seemed to increase in the 12 G-series.

In the 60G-series the plasma Na, K and Cl concentrations fell to values not differing significantly

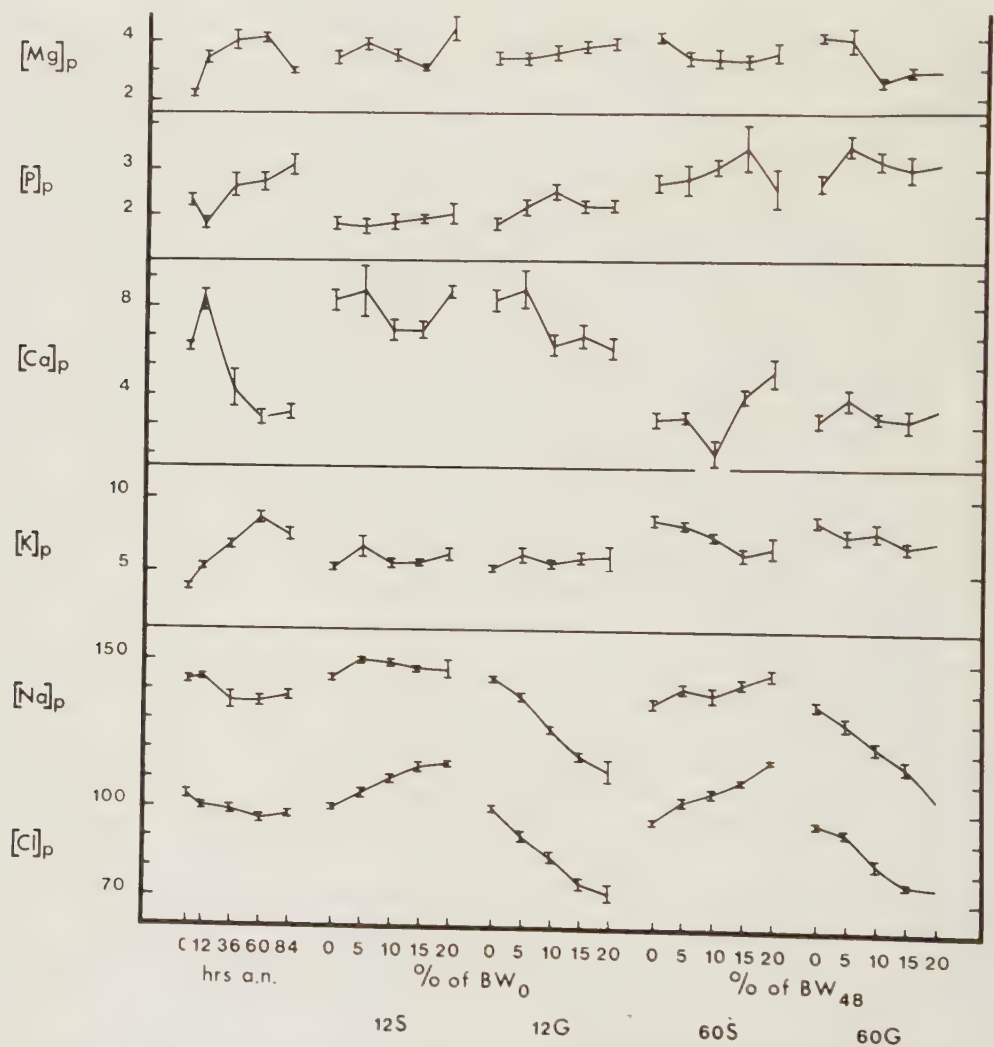


FIG. 4. Effect of nephrectomy and nephrectomy plus overhydration on some plasma electrolyte concentrations. The plasma inorganic phosphorus concentration is expressed in mmol/l plasma, the other plasma electrolyte concentrations in mEq/l plasma. For further explanation, see fig. 1.

from those calculated from the expansion of the extracellular volume ($^{51}\text{Cr-EDTA}$).

The increase in the extracellular amount of K in the 12G-series was of the same magnitude as the decrease of the K content of the RCV_B . The increase in the extracellular amount of Na and Cl, as calculated from the change in ECW_B^{Cr} , seemed to be due mainly to an overestimation of the true ECW_B increase (see Total body).

Osmotic haemolysis was noted also in the 60G-series, but it did not produce any significant increase in the extracellular amount of K. It is, however, possible that more K was bound to the intracellular space in association with the glucose entrance and the glycogen synthesis in this series than in the 12G-series, since the animals had been deprived from food and water longer than the animals in the 12G-series.

PLASMA CALCIUM, MAGNESIUM AND INORGANIC PHOSPHORUS (Fig. 4)

C-12 hrs. The plasma Ca and Mg concentrations were considerably higher in the 12hr-series than in the controls. On the other hand, the plasma phosphorus concentration was nearly significantly lower in the 12hr-series than in the controls.

That the plasma Ca concentration increases transiently after nephrectomy in mammals has been shown earlier (Elliot & Freeman 1956, Freeman & Chang 1950, Simpson 1963). The elimination of parathyroid hormone is prolonged after nephrectomy (Martin et al. 1969) and signs of increased parathyroid and osteoclast activity have been reported to occur early after nephrectomy (see Jastak et al. 1968). The increase of the plasma Ca concentration is accompanied by a rise of the plasma citrate level, and it has therefore been assumed that it is the complex-bound ultrafiltrable fraction of the plasma Ca that increases. The elevation of the citrate is relatively greater than that of Ca. No explanation could be offered for the initial fall of the plasma phosphorus concentration in the present study. Jastak et al. (1968) found that the plasma phosphorus concentration increased during the first 12 hrs after nephrectomy in rats.

A raised plasma Mg concentration in acute renal failure and after nephrectomy in experimental animals has been reported by many authors (see Maher and Schreiner 1961). An increased plasma citrate concen-

tration during the initial phase after nephrectomy might have contributed to the relatively marked rise of the plasma Mg concentration found in the present study, as it did to that of Ca.

Gitelman et al. (1968) found that a subcutaneous injection of isotonic MgCl_2 immediately after nephrectomy in rats gave a hypermagnesaemia and a depressed total, complexed and ionic plasma Ca concentration 3.5 hrs later. They ascribed these later effects of the hypermagnesaemia to an inhibition of the parathyroid function. Such interactions between the plasma Mg and Ca concentrations might have been brought into play and contributed to the results observed in the present investigation.

12–84 hrs. During the 12–84 hour period after nephrectomy the plasma Ca concentration fell to subnormal levels, while the plasma phosphorus concentration rose to abnormally high values, as expected.

The plasma Mg concentration, however, continued to rise somewhat until 60 hrs after nephrectomy, after which it fell considerably. This final decrease of the plasma Mg concentration could not be explained. A similar fall was noted also for the plasma K concentration (see above).

12S and 60S and 12G and 60G. The plasma Mg concentration fell in the 60S and 60G-series. The fall in the 60G-series was nearly significantly larger than in the 60S-series. No change in this variable could be demonstrated in the 12S and 12G-series.

The plasma Mg concentration thus varied in largely the same way as the plasma K concentration in the overhydrated animals. Since these two ions are the main intracellular cations, this observation was interesting.

That the plasma Mg concentration fell more in the 60G than in the 60S-series may, perhaps, be explained by the glucose entrance into the cells (Briggs et al. 1923–24, Aikawa 1960, Williams et al. 1966).

The plasma Ca concentration rose nearly significantly in the 60S-series, while no clear-cut change of this concentration could be demonstrated in the 12S-series. The plasma Ca concentration fell significantly in the 12G-series, but not in the 60G-series.

The plasma phosphorus concentration rose nearly significantly in the 12G-series. Also in the other three series the plasma phosphorus tended to increase. It is clear from the figure that these changes were not linear in the 60S and 60G-series.

In the evaluation of the plasma Ca concentration

the plasma protein concentration, which decreased in all four series, must be taken into account. This decrease of the plasma protein naturally gives greater weight to the increase of the plasma Ca concentration in the 60S-series.

The changes in plasma Ca and phosphorus concentrations in the overhydrated series are difficult to evaluate because only the total plasma Ca concentration was determined.

That plasma Ca concentration increased in the 60S and did not decrease in the 60G-series suggests that the extracellular amount of Ca increased in these two series and might have contributed somewhat to bind water osmotically to this space.

The mean values found for the blood and plasma variables in the controls did not differ appreciably from those observed by others in the normal rabbit (Manery & Hastings 1939, Manery & Bale 1941, Aikawa 1950, Muirhead et al. 1952, Albritton 1953, Manery 1954, Elliot & Freeman 1956, Aikawa 1960, Bradbury et al. 1968).

RED CELL ELECTROLYTE CONCENTRATIONS (Fig. 5)

C-12 hrs and 12-84 hrs. The red cell Na and K concentrations and the calculated red cell Cl concentration in the controls were in good agreement with the values given by Bernstein (1954). The red cell Na concentration fell nearly significantly initially after nephrectomy, to rise during the 12-36 hr period and to persist at a higher level than that in the control series. The red cell K concentration increased nearly significantly initially after nephrectomy and afterwards fell linearly by about 7 mEq/l red cells per 24 hrs. The ratio C_{rc}^{Br} / C_p^{Br} increased continuously from 0.47 ± 0.01 to 0.64 ± 0.01 during the period studied after nephrectomy. This means that the red cell Cl concentration should have increased from 49 to 62 mEq/l red cells, since Cl and Br distribute themselves equally over the erythrocyte membrane (Weir & Hastings 1939, Gamble & Robertson 1952, Sweet et al. 1957). The calculated changes in the amount of electrolytes of the RCV_B during the period 12-84 hrs after nephrectomy were as follows: Na ± 0.0 , K - 1.1 and Cl - 0.2 mEq/kg BW₀.

Several investigators have found the red cell sodium concentration often to be raised in uraemia (Gessler 1961, Bock et al. 1962, Welt et al. 1964, Gessler &

Planz 1965, Jahrmärker 1967, Welt et al. 1967, Welt 1969, Smith et al. 1970), but low concentrations have also been reported (Czackzkes et al. 1967). Also data on the red cell potassium concentration in uraemia differ. Thus low (Bock et al. 1962), normal (Hutt 1952, Giovanetti et al. 1965, Czackzkes et al. 1967) and high values (Gessler 1961) have been reported. Biro (1968) found, as in the present study, a considerable decrease in the red cell K concentration and an increase in the red cell Na concentration in rats 2-3 days after nephrectomy. Since several disturbances in the erythrocyte metabolism have been found in uraemia (see Bergström & Bittar 1969) it appears but natural to ascribe the electrolyte changes partly to these metabolic alterations.

Bock et al. (1962) found that the energy-metabolism was defective in the red cells of patients with chronic uraemia, mainly because of a reduced hexokinase activity. The ATP concentration was reduced and with it also the access to energy for the glycoside-inhibitable sodium pump. The reduction of hexokinase activity was thought by Bock et al. (l.c.) to be due mainly to a low intracellular pH. Lichtman et al. (1970), however, obtained different results. They observed an increased red cell ATP concentration in uraemia and a highly significant correlation between the red cell ATP concentration and the serum phosphorus. They also found a normal amount of ATP ase in uraemic red cells.

Welt (1969) showed that the elevated red cell sodium concentration in uraemia was a consequence of a defect in both the glycoside-inhibitable and the ethacrynic acid-inhibitable sodium pump. The defect in the glycoside-inhibitable sodium pump was not due to lack of ATP, but to a reduced alkaline metal sensitive ATPase activity. The defective ATPase activity could be normalised by haemodialysis.

In the present study the red cell Na and K concentration appeared to decrease and increase, respectively, initially after nephrectomy at the same time as the red cell water content tended to increase. This presumably means that the red cell Na content did not change while the red cell K content increased. This might be explained by the elevated plasma K concentration which could have initiated an increased ion transport via the glucoside-inhibitable sodium pump (Sachs & Welt 1967, Welt 1969).

That the red cell Na and K concentration increased and decreased, respectively, during the 12-84 hr period after nephrectomy could not be ascribed to

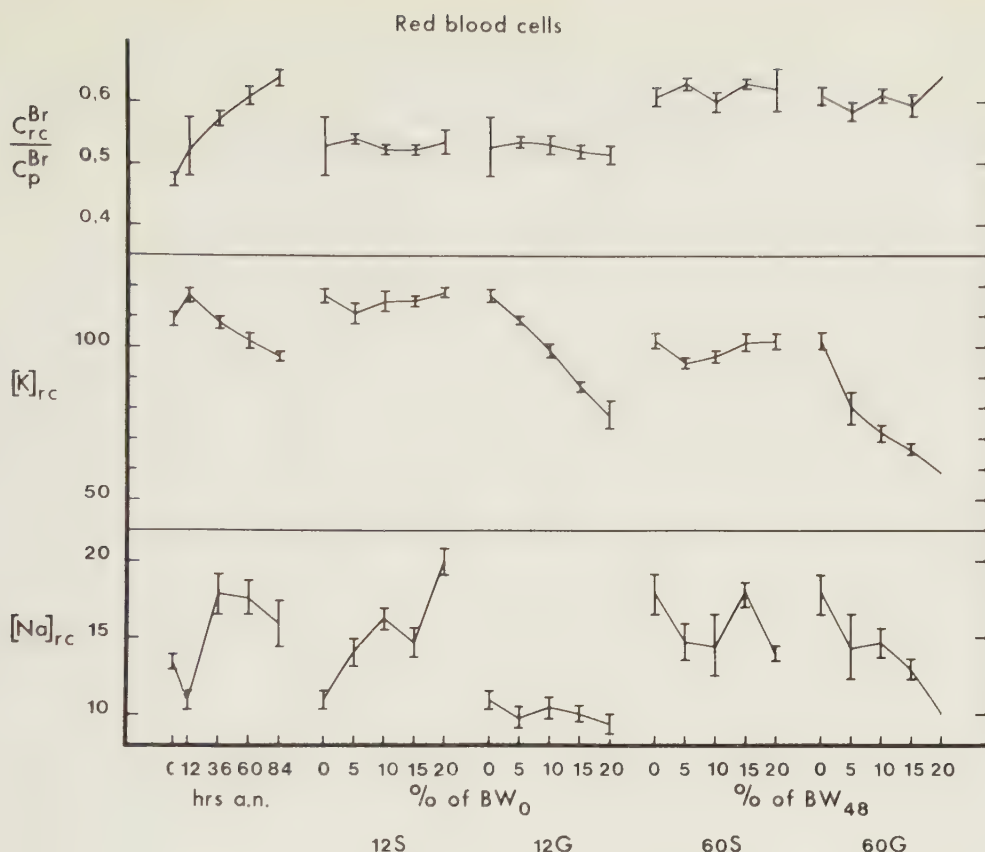


FIG. 5. Effect of nephrectomy and nephrectomy plus overhydration on the red blood cell Na and K concentration (mEq/l red cells) and the $\frac{C_{rc}^{Br}}{C_p^{Br}}$ ratio. For further explanation, see fig. 1.

changes in the degree of hydration of the erythrocytes or to changes in the plasma Na and K concentrations, both of which changed in the opposite direction. The changes observed must therefore be ascribed to a decreased red cell K-binding capacity (inter alia because of increased acidosis), a decreasing activity of the the Na-K-pump and/or an increase of the red cell membrane permeability to Na and K.

The increasing $\frac{C_{rc}^{Br}}{C_p^{Br}}$ ratio was probably due, above all, to decreasing pH (Harris & Maizels 1952). The calculated red cell Cl concentration increased by about 13 mEq/l red cells during the period studied, while the red cell Na + K-concentration decreased by about 24 mEq/l red cells. A shift of other ions not determined had thus occurred at the same time. Here must, in the first place, the increasing acidosis be taken under consideration.

12S and 60S. The red cell Na concentration increased considerably in the 12S-series. Otherwise no significant changes occurred in the two series.

That the $\frac{C_{rc}^{Br}}{C_p^{Br}}$ ratio did not change would imply that the red cell Cl concentration increased from 53 to 60 mEq/l red cells in the 12S-series and from 58 to 72 mEq/l red cells in the 60S-series. The calculated changes in the amount of electrolytes of the RCV_B were as follows: In the 12S-series: Na + 0.15, K - 0.5 and Cl - 0.1 mEq/kg BW_0 and in the 60S-series: Na - 0.1, K - 0.3 and Cl $\pm$ 0.0 mEq/kg BW_{48} .

Why the red cell Na concentration increased considerably in the 12S-series is at present obscure. The small increase in the plasma Na concentration could by no means explain the large increase in the red cell

Na concentration in this series. In the 60S-series the saline overhydration may have caused an increased active Na — K transport or a decrease in the permeability of the red cell membrane to Na and K, since the plasma Na and K concentration increased and decreased, respectively, at the same time as the red cell Na and K concentrations remained unchanged. One might explain this phenomenon by the assumption that overhydration caused dilution and/or correction of some toxic factors for the Na — K pump activity or permeability.

The red cell Na and Cl concentrations increased to roughly the same extent in the 12S-series, but not in the 60S-series, which means that in the latter there must have been a change in the concentration of some other ions, not determined.

12G and 60G. The red cell K concentration decreased considerably in both the 12G and 60G-series, like the red cell Na concentration in the 60G-series. The red cell Na concentration fell also in the 12G-series, but only numerically. The C_{rc}^{Br} / C_p^{Br} ratio did not change in the 12G or the 60G-series, which means that the red cell Cl concentration should have decreased from about 53 to 37 mEq/l red cells in the 12G-series and from about 58 to 45 mEq/l red cells in the 60G-series. In the two series the red cell water content appeared to increase, since the red cell Hb concentration fell.

The calculated changes in the amount of electrolytes of the RCV_B were of the following magnitudes: In the 12G-series: Na — 0.1, K — 1.3 and Cl — 0.4 mEq/kg BW₀ and in the 60G-series: Na — 0.1, K — 1.2 and Cl — 0.4 mEq/kg BW₄₈.

In both the 12G and the 60G-series the decreases in the red cell K concentrations were relatively larger than that in the plasma K concentration, and the decrease in the Na concentration was relatively smaller than that in the plasma Na concentration. This suggests that the observed decrease in the red cell Na and that in the K concentration were an effect not only of dilution, but also of decreased activity of the Na—K pump, decreased K-binding capacity and/or an increased permeability to these two ions.

In the two series the red cell Na + K concentration fell substantially more than the red cell Cl concentration. In the 12G-series, the red cell Na + K concentration fell by about 24 mEq/l red cells more than did the red cell Cl concentration. The corresponding

figure for the 60G-series was as high as 41 mEq/l red cells. This discrepancy can be ascribed in part to the observed decrease of the red cell Hb concentration. Changes probably occurred also in the red cell concentration of other non-determined ions.

FREE BODY FLUIDS (FBF) (Fig. 6)

C—12 hrs. During the first 12· hrs after nephrectomy the amount of ascitic fluid tended to decrease and the amount of pericardial effusion diminished almost significantly, while the amount of pleural effusion persisted unchanged.

That the amount of ascitic fluid did not increase might be taken as evidence that the nephrectomy caused only a slight trauma. If the operation had been followed by a severe post-traumatic inflammation at the site of the kidney, close to the peritoneal cavity, a local increase of permeability would presumably lead to an increased amount of ascitic fluid.

12—84 hrs. During the 12—84 hr period after nephrectomy no significant change was observed in the variables studied, but, as is apparent from Fig. 6, the amount of ascitic fluid tended to increase somewhat and then hyperbolically, as did the amount of pericardial effusion. This hyperbolic increase of the amount of ascitic fluid and pericardial effusion may mirror the changes in ECW_B, but also other factors were with certainty involved (changes in capillary pressure, respiration, intestinal motility and capillary permeability, the last mentioned because of uraemic enterocolitis, gastritis, pneumonitis and pericarditis, respectively).

Lindqvist (1964) reported that the amount of ascitic fluid, pleural and pericardial effusion increased after bilateral ureteric ligation in rabbits allowed food and water *ad lib.*. The increase in the amount of ascitic fluid and pleural effusion was much greater than in the present series. This discrepancy may be due to transudation of urine into the peritoneal cavity from the renal pelves and the ureters. In a preliminary study where the extracellular volume was determined with ¹³¹I-propylinulin in rabbits after bilateral ureteric ligation, the concentration of ¹³¹I-propylinulin was much higher in the ascitic fluid than in the plasma (unpublished personal observations).

12S and 60S. The amount of ascitic fluid increased more in the 12S-series than in the 60S-series. The difference in the increase of the amount of pleural effusion between the two series was much smaller and not significant. In none of the series did the amount of

pericardial effusion increase. It was unexpected that the amount of ascitic fluid increased less in the 60S than in the 12S-series, especially since the animals in the 60S-series probably had changes due to enterocolitis.

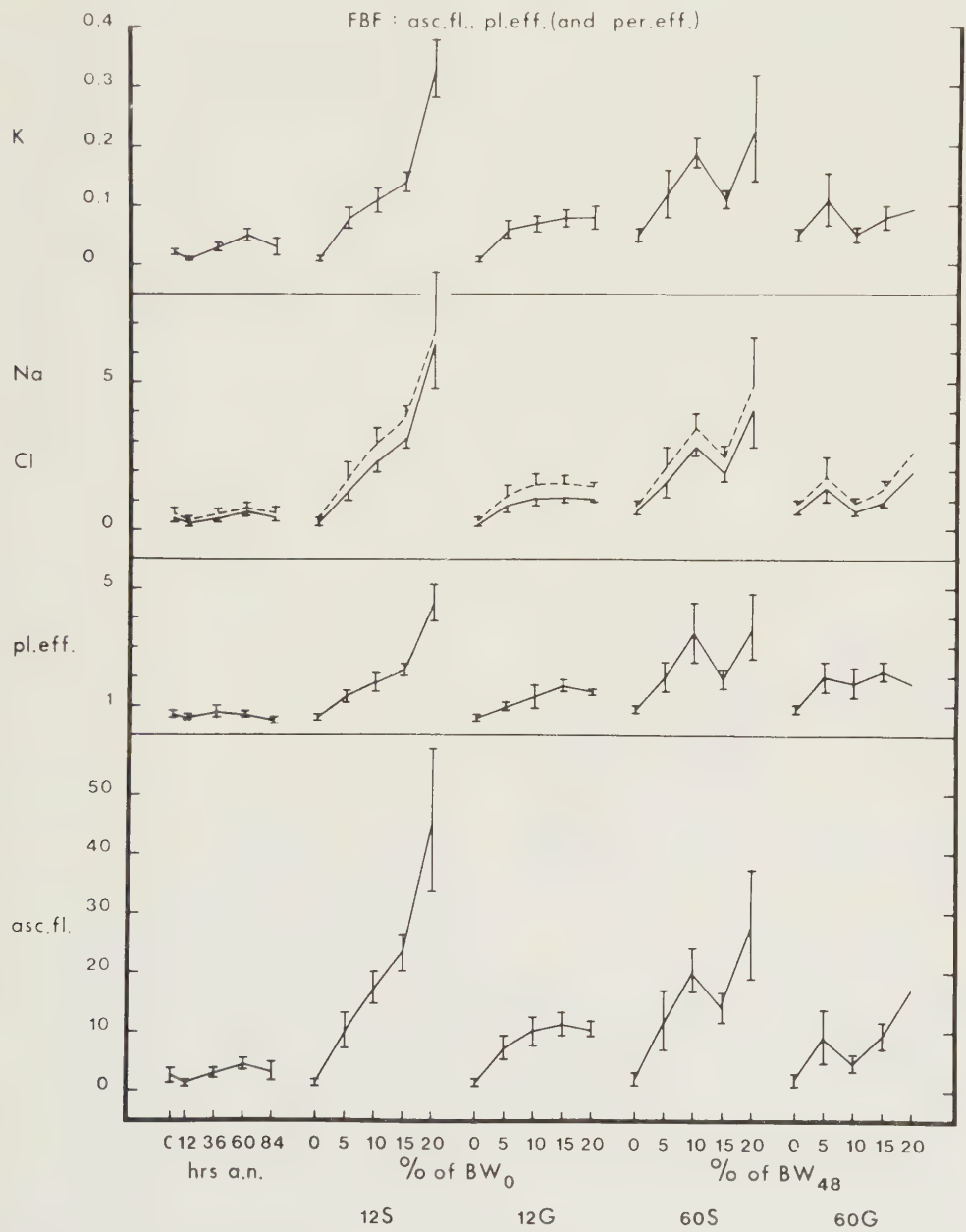


FIG. 6. Effect of nephrectomy and nephrectomy plus overhydration on the amount of ascitic fluid, pleural effusion and electrolytes in the free body fluids (ml or mEq/kg BW₀ and BW₄₈). For further explanation, see fig. 1.

Lindqvist (1964) found the opposite correlation between the degree of uraemia and the volume of ascitic fluid in rabbits with both ureters ligated and overhydrated to 15% of bodyweight with Ringer solution compared with the present study. The pleural effusion increased in his study to values of about the same magnitude as those found in the corresponding groups of the present study.

12G and 60G. The increase in the amount of ascitic fluid and pleural effusion in the 12G-series was one third and one half, respectively, as large as in the 12S-series. The increase in the amount of ascitic fluid was numerically half as large in the 60G as in the 60S-series.

The amount of ascitic fluid and pleural effusion in the 12G-series and the amount of pleural effusion in the 60G-series seemed to increase hyperbolically. No clear difference was found between the 12G and 60G-series regarding the magnitude of the size of the increase of ascitic fluid and that of pleural effusion. The amount of pericardial effusion did not increase significantly in either of the two glucose-overhydrated series.

Since the difference between the 12G and 60G-series and between the 12S and 60S-series seemed to be of the same magnitude regarding the increase in ECW_B , one might have expected that the increase in the amount of ascitic fluid would have been larger in the 12G than in the 60G-series (see 12S and 60S-series).

Lindqvist (1964) overhydrated rabbits with 5.5% glucose solution to 15% of the bodyweight 48 hrs after bilateral ureteric ligation and 24 hrs later he found no increase in the amount of ascitic fluid, but a considerable increase in the pleural effusion. As mentioned above, the experimental conditions were, however, not identical.

SKIN (Fig. 7)

C-12 hrs and 12-84 hrs. The composition of the skin preparations studied was complex. It included the hair, the epidermis with hair follicles and sebaceous glands, the corium with connective and fat tissue, the superficial fascia, and the paws and the ears with some bone, cartilage and muscle tissue. The results are therefore not strictly comparable with those reported in the literature. Since the electrolyte-fluid distribution in connective tissue, the most predomnant tissue in the preparation, is not yet properly known (see Langgård 1956), the findings are difficult to interpret.

As in most of the tissue studied, ECW^{Br} was larger than ECW^{Cl} . It could not be decided whether this was a true difference or simply due to underestimation of the Cl content (see Cotlove 1963). ECW^{Cr} was less than ECW^{Cl} in the 12 hr-series, but this relationship was not true throughout the period studied after nephrectomy. ECW^{Cr} can therefore not be regarded as a suitable variable for estimating the changes in the true ECW of the preparation in all situations (see also below). No significant differences were found between the controls and the 12 hr-series regarding the variables studied, but the K and water content tended to increase and decrease, respectively.

During the 12-84 hr period after nephrectomy the skin lost significant amounts of water, Na and K, while the amount of Cl tended to decrease hypobolically, and the ECW, measured with the three reference substances, tended to increase hyperbolically. ECW^{Br} exceeded the total amount of water in the skin during the 36-84 hr period after nephrectomy. The amount of FFS did not change.

That ECW tended to increase may have been due to a decreasing extra-intracellular gradient of the reference substances used and possibly also to an increasing binding of the reference substances to extracellular substances. That especially Br is to some extent bound to some structures in the skin is apparent from the observation that ECW^{Br} exceeded the total amount of water at the end of the period studied.

The loss of Na + K was relatively larger than that of water. This might be partly explained by the assumption that H-ions were bound to intra- and extra-cellular polyanions and displaced Na and K. The loss of K from the intracellular compartment and perhaps also of extracellularly bound K must have been larger than the total loss observed since the amount of K in the free interstitial fluid must have increased. The extracorporeal amounts of electrolytes in the skin preparation can hardly have changed to any notably extent during the period studied.

Aach et al. (1957) studied the effect of nephrectomy and fasting on water gains and losses in rats. They found, in contrast with the observations made in the present study, that the skin gained water during a period of 48 hrs after nephrectomy. This discrepancy may be explained by the fact that their rats had free access to water after nephrectomy.

12S and 60S. In the saline overhydrated series the weight of the skin, the amount of water and ECW measured with the three reference substances increased

markedly. No significant differences were found in the magnitude of the respective increases between the two series.

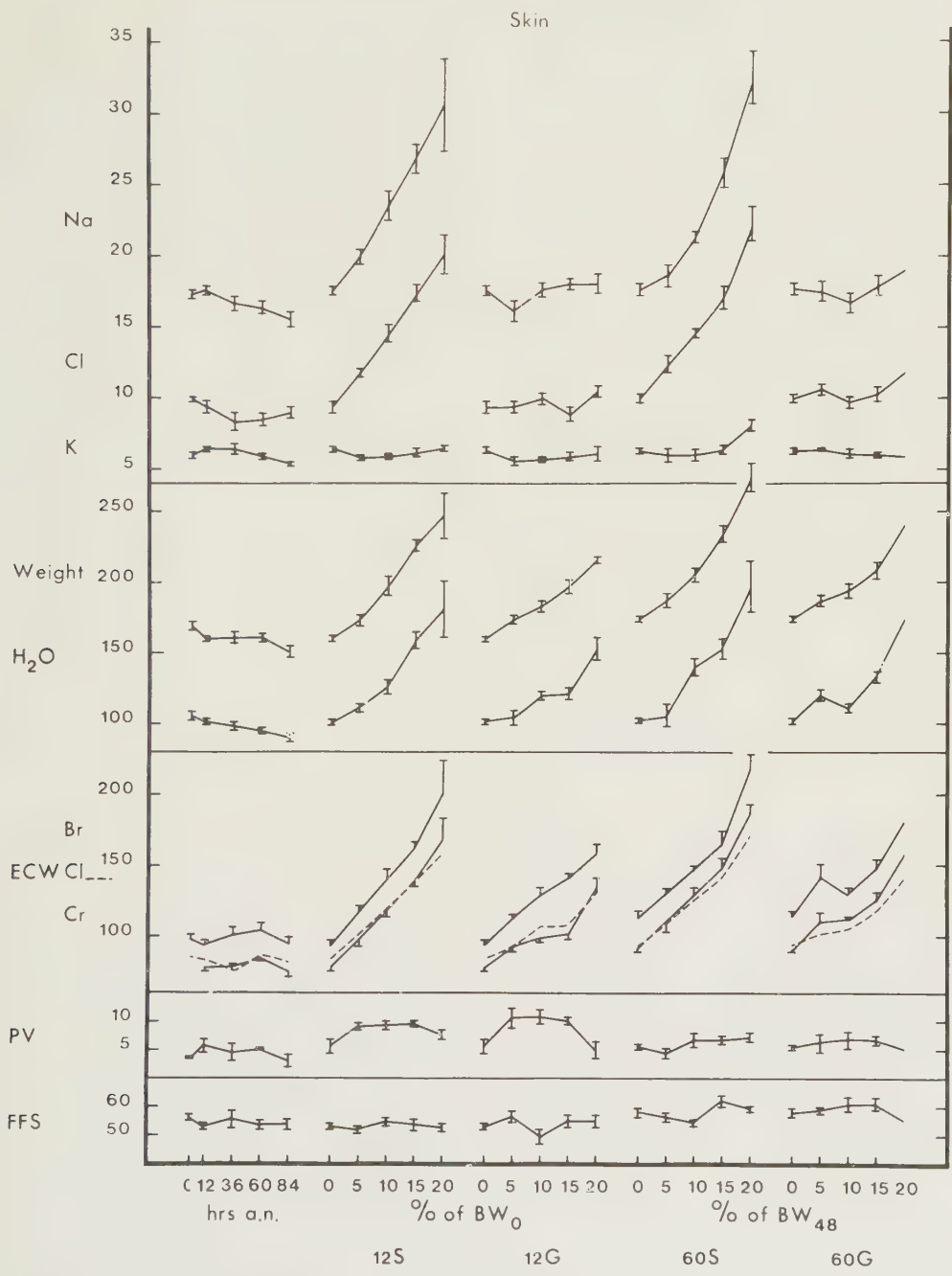


FIG. 7. Effect of nephrectomy and nephrectomy plus overhydration on the skin variables studied (ml or mEq/kg BW₀ and BW₄₈). For further explanation, see fig. 1.

In the 12S-series as well as in the 60S-series the ECW^{Cl} increased numerically less than did the amount of water, in contrast with what was noted for ECW^{Br} and ECW^{Cr} , which, especially in the 12S-series, tended to increase more than the amount of water. In the 12S-series the difference between the increase of ECW^{Cl} and ECW^{Br} was significant ($p < 0.01$). Since similar changes were also found in the two glucose overhydrated series the above discrepancies can hardly be ascribed to chance. The increase in the water content of the skin was presumably due to an increase of only the extracellular water, an assumption substantiated by the above mentioned findings (ECW^{Cl} excepted).

A certain intracellular dehydration may also have occurred in the 12S-series since ECW^{Br} and ECW^{Cr} increased numerically more than did the amount of water in this series. In the 60S-series the latter difference was less marked, which suggests that the intracellular volume did not change to any appreciable extent in this series.

The amount of Na and Cl in the skin increased equally in the two series, and the magnitudes of the increase were the same in the 12S as in the 60S-series. The K content of the skin was not significantly affected by saline overhydration. In the 12S-series the extracellular amount of K must have increased since the extracellular volume increased without any corresponding fall in the concentration of extracellular K.

Skelton (1927) ligated the ureters in cats and overhydrated the animals with distilled water to 2.5% of the bodyweight and with 0.9% NaCl solution to 2% of the bodyweight, respectively, and found a water increase in the skin. The water increase was larger following saline hydration than following overhydration with distilled water, a finding compatible with observations in the present study (see below).

12G and 60G. As expected, the weight of the skin, the amount of water and the ECW measured with the three reference substances increased considerably less during glucose overhydration than during saline overhydration. As for the magnitude of the increases, no significant difference was found between the 12G and the 60G-series.

The relationship between the increase of ECW^{Cl} , ECW^{Br} and ECW^{Cr} was largely the same as on saline overhydration, i.e. $ECW^{Cl} < ECW^{Cr} \leq ECW^{Br}$. In

the 12G-series the ECW^{Cl} and the amount of water increased equally numerically, while the ECW^{Br} increased significantly, ($p < 0.01$) and the ECW^{Cr} numerically, more than did the amount of water. The latter difference suggested dehydration of the intracellular space of the skin, which, however, appears unlikely. That the ECW^{Br} and the ECW^{Cr} increased more than the amount of water must instead be explained by the assumption that the concentration of ^{82}Br and ^{51}Cr -EDTA in some of the extra- and/or intracellular phases of the skin did not fall to the same extent as in plasma.

In the 60G-series the ECW^{Cl} increased numerically less than did the amount of water, while ECW^{Br} and ECW^{Cr} increased numerically to the same extent as the water. Also in this series the intracellular space of the skin had probably increased. That this is not reflected in the ratio between the increase of the amount of water and ECW^{Br} and ECW^{Cr} , respectively, in the skin, may be explained in the same way as in the 12G-series (see above) and in part by difficulties in demonstrating changes in the intracellular space in a tissue where the extracellular space is predominant.

The amounts of Na, K and Cl in the skin did not change significantly in the two glucose overhydrated series.

In the 12G-series the extracellular amount of K must have increased, but this increase was relatively small and it was masked by a reduction of the amount of K in the RCV of the skin.

GASTRIC CONTENTS (Fig. 8)

C-12 hrs. The weight of the gastric contents and DV^{Cr} were nearly significantly larger and the DV^{Br} significantly larger 12 hrs after nephrectomy than in the controls. The mean differences were 11.6 g, 0.6 ml and 20.9 ml/kg BW₀, respectively.

These differences might have been due to an increase in the secretion of gastric juice, a reduction in the gastric emptying rate and/or increased secretion of saliva. The possibility of an increased gastric secretion gains force from the fact that the difference between the 12 hr and the control series was larger for the DV^{Br} than for the weight and that the DV^{Cl} , the DV^{Br} and the Cl content of the stomach tended to be larger in the 12 hr-series than in the controls. The

probability that the gastric emptying rate was lower in the 12 hr-series is supported by the finding that the weight and the water content of the intestinal preparation tended to be smaller for the 12 hr-series than for the controls.

12–84 hrs. Autopsy invariably revealed residual food in the stomach.

The weight and the DV^{Br} of the gastric contents diminished by 21 g and 31 ml per kg BW_0 , respectively, during the 12–36 hr period after nephrectomy, but only by about 5 g and 8 ml per kg BW_0 , respectively, during the rest of the experimental period. The DV^{Cr} of the gastric contents remained unchanged during the entire period. No significant ^{125}I -activity could be observed in the gastric contents.

After cessation of the supposed postoperative inhibition of emptying of the stomach an increase in acidity and amount of gastric contents may have stimulated the emptying of the stomach to such an extent as to explain the marked reduction of the weight and

the DV^{Br} of the gastric contents during the 12–36 hr period after nephrectomy. That assumption is supported by the observation that the weight, the water, the Na and the K content of the intestinal preparation did not diminish during the period in question.

Since the DV^{Cr} of the gastric contents did not decrease with the weight, the ^{51}Cr -EDTA concentration increased. This increase might be explained by the uraemic gastritis with increased permeability of the mucosa to ^{51}Cr -EDTA.

12S and 60S. The weight and the DV^{Br} of the gastric contents in the 12S-series like the change in the weight, the water and the Na content of the intestinal preparation tended to increase initially and then to decrease markedly.

In the 60S-series the weight and the DV^{Br} of the gastric contents did not change. The DV^{Cr} was unchanged in the two saline-overhydrated series.

12G and 60G. The weight and the DV^{Cr} of the gastric contents did not change in either of the glucose

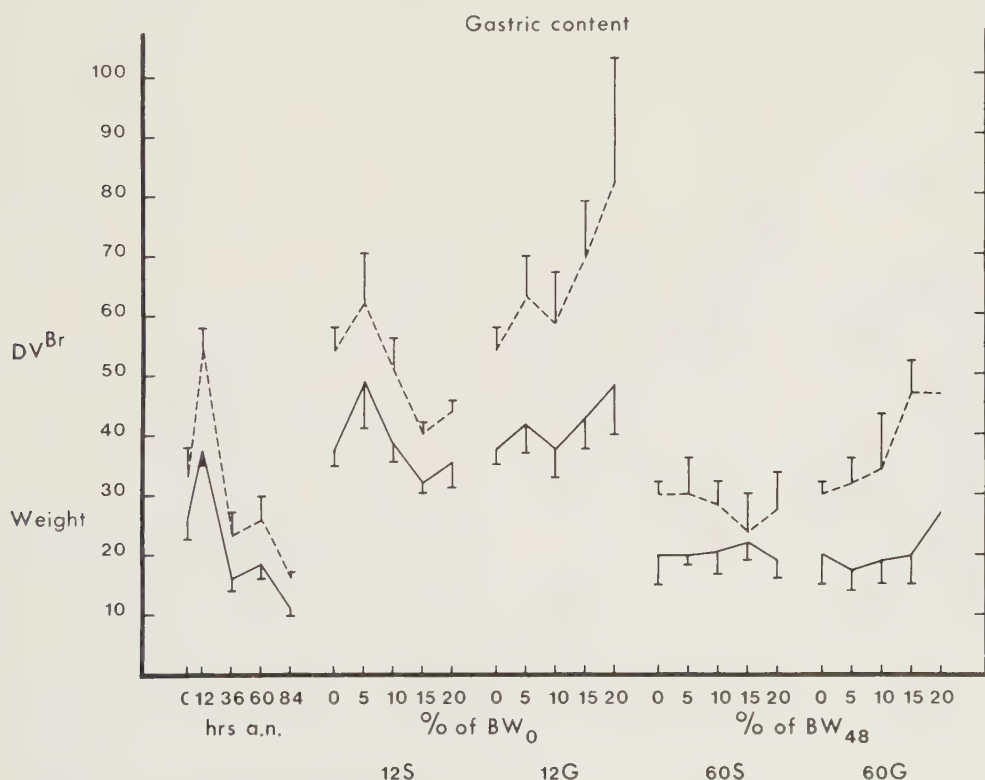


FIG. 8. Effect of nephrectomy and nephrectomy plus overhydration on the weight and DV^{Br} of the gastric contents (g or ml/kg BW_0 and BW_{48}). For further explanation, see fig. 1.

overhydrated series. In both of them, however, the DV^{Br} tended to increase possibly because of increased secretion of gastric juice and/or saliva. The secretion of saliva was obviously increased during infusion of the glucose solution in these two series (compare Lindqvist 1964).

The assumption that the saline and/or the glucose overhydration influenced the secretion of gastric juice and saliva and/or emptying rate of the stomach is supported by the significant difference found between the 12S and 12G-series concerning the b-values of the linear regression equation for DV^{Br} .

STOMACH (Fig. 9)

C-12 hrs. The DV^{Cl} was nearly significantly, and the DV^{Br} and the Cl content of the stomach were numerically, larger in the 12 hr-series than in the controls. The amount of FFS, on the other hand, was nearly significantly smaller in the 12 hr-series than in the controls. Otherwise, no remarkable differences were found between the controls and the 12 hr-series. The tendency of the DV^{Cl} , the DV^{Br} and the Cl content of the stomach to increase initially after nephrectomy might be explained by an increased gastric secretion (see also Gastric contents).

12–84 hrs. None of the animals in the 12 hr-series, one (10%) in the 36 hr-group, five (30%) in the 60 hr-group and four (30%) in the 84 hr-group showed gross signs of gastritis (red, swollen mucosa) at autopsy. The weight, water, Na- and Cl-content as well as the DV^{Cl} , DV^{Br} and DV^{Cr} did not change during the 12–36 hr period after nephrectomy but afterwards increased markedly. No significant differences were found in the magnitude of the increase of the various fluid variables. The K content diminished during the 12–36 hr period and persisted at a relatively low level.

The changes found agree well with the assumption that the uraemic gastritis had produced extracellular oedema in the stomach. It appears reasonable to assume that also the inflammation contributed to cellular oedema though it is not apparent from the results probably because of a certain degree of cellular destruction and/or an increased relative intra and/or transcellular Cl, ^{82}Br and ^{51}Cr -EDTA concentration (compare the fact that the ^{51}Cr -activity of the gastric contents increased). That the K-content of the stomach

decreased during the 12–36 hr period after nephrectomy and then persisted at a relatively low level despite the increase in the extracellular amount of K suggested that cells had been damaged. The assumed loss of intracellular K did not seem to be compensated by an increase in the intracellular amount of Na, since the calculated extracellular amount of Na according to the DV^{Cr} increased numerically more than the total Na content of the stomach. The changes found are compatible with the microscopical findings of Orbinson et al. (1952) in nephrectomised dogs and by Churg & Paterson (1963) in nephrectomised rats. These authors observed oedema, haemorrhages, necrosis, cytolysis and an inflammatory reaction with polymorphonuclear infiltration in the stomach some days after nephrectomy. The considerable increase of the DV^{Cr} of the stomach, might be used as an objective measure of the gastritic changes in the search for aetiological factors in uraemic gastritis.

12S and 60S. None of the animals in the 12S-series and only three (13%) of the 23 overhydrated animals in the 60S-series showed gross gastritis at autopsy. In the 12S-series DV^{Cr} increased significantly, while DV^{Cl} and DV^{Br} increased only numerically. The water content increased nearly significantly, but only half as much as DV^{Cr} . Further, the Na and the Cl content increased significantly and numerically, respectively, while the K content did not change with certainty.

In the 60S-series the weight, the water, Na, K and Cl content as well as the DV^{Cl} , DV^{Br} and DV^{Cr} increased considerably, but not before 10–15% overhydration. The increases were much larger than those in the 12S-series. As in the 12S-series, the DV^{Cr} seemed to increase more than the water content in the 60S-series.

As expected, the extracellular space in the stomach increased on saline overhydration. It is not known with certainty whether any simultaneous intracellular dehydration occurred, though the numerical difference between the increase of DV^{Cr} and the water content, especially in the 12S-series suggests that it did. That the fluid variables in the stomach increased much more in the 60S-series than in the 12S-series, though the ECW_B appeared to increase more in the 12S than in the 60S-series, was probably due to the presence of gastritis in the 60S-series.

Only a small fraction of the observed increase of

the K content in the 60S-series could be ascribed to an increase in the extracellular amount of K of the preparation. The intracellular amount of K therefore probably increased.

12G and 60G. None of the animals in the 12G-series and only three (13%) of the 23 overhydrated

animals in the 60G-series showed gross gastritis at autopsy. The water content, DV^{Cl} , DV^{Br} and DV^{Cr} of the stomach increased in the 12G-series largely linearly. In the 60G-series, as in the 60S-series, these variables increased hypobolically. No significant difference was found between the 12G and 60G-series

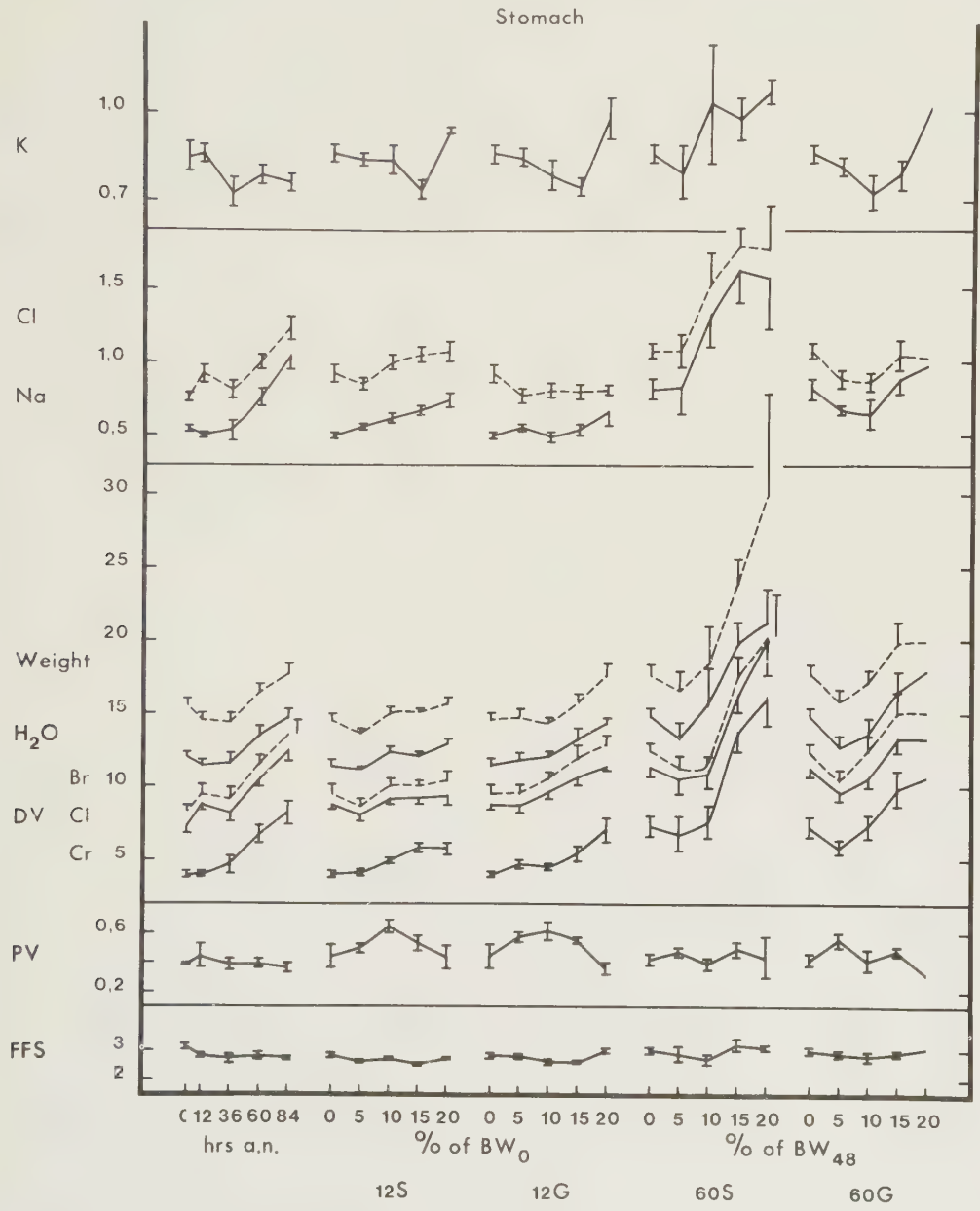


FIG. 9. Effect of nephrectomy and nephrectomy plus overhydration on the stomach variables determined (g, ml or mEq/kg BW₀ and BW₄₈). For further explanation, see fig. 1.

in the magnitude of the increases. The Na, K and Cl content of the stomach did not change in any particular way in either of the series. The water content of the stomach increased twice as much in the 12G-series as in the 12S-series while the DV^{Cr} increased equally in both series.

The weight increased significantly, DV^{Cl} , DV^{Br} and DV^{Cr} nearly significantly, and the water content increased numerically less, in the 60G than in the 60S-series.

The glucose overhydration could be expected to increase both the extra and the intracellular space of the stomach. The reason why no intracellular increase could be determined with the aid of the variables measured might have been that the relative reduction of the intra and/or the transcellular Cl, ^{82}Br and ^{51}Cr -EDTA concentration was not proportional to the extracellular reduction (compare the tendency for the ^{82}Br -activity in gastric content to increase).

THE INTESTINAL PREPARATION (Fig. 10)

C-12 hrs and 12—84 hrs. As in earlier investigations it was not possible to determine how the water, Na, K and Cl were distributed between the extracellular, the intracellular and the transcellular compartments of the gut. Determination of the water and of the electrolyte content of the intraluminal compartment is technically difficult. Gotch et al. (1957) found the following values for the intraluminal content of water and electrolytes in the whole gastrointestinal tract in male rabbits weighing about 2 kg: water 90 ml, Na 6.8 mEq, K 3.5 mEq and Cl 5.6 mEq/kg BW, *i.e.* considerable amounts compared with the TBW, TBNa, TBK and TBCl. In the present investigation these sources of error in the determination of the body variables were somewhat reduced by not including the intraluminal content of the stomach in the calculation of TBW, TBNa, TBK, TBCl, etc. This implies, for example that ECW^{Br} was reduced by 11% in the control series. It should be observed that the exclusion of the gastric contents did not include elimination of the transcellular fluid in the gastric glands.

The Br/Cl quotient has been found to be lower in plasma than in saliva and gastric juice (Mason 1936, Gamble et al. 1953, Staffurth & Birchall 1960). This was found to hold also in the stomach preparation

in the present study: the DV^{Br} was clearly larger than the DV^{Cl} . In the intestinal preparation DV^{Br} tended to be larger than DV^{Cl} , but the difference was small.

^{51}Cr -EDTA seemed to be a satisfactory marker for measuring the extra-cellular volume of the stomach wall. The small but significant amount of ^{51}Cr -EDTA observed in the gastric contents might have passed through the gastric mucosa, but some of it may also have derived from the saliva. In the intestinal preparation ^{51}Cr -EDTA was found to measure an equally large space as Cl and ^{82}Br , *i.e.* ^{51}Cr -EDTA overestimates the extracellular volume in this preparation. Hence the intraluminal space in the intestines might have received ^{51}Cr -EDTA via the saliva, the gastric secretion and/or the bile (In a pilot study it has been found that the ^{51}Cr -activity was just as high in bile as in plasma) or a penetration of ^{51}Cr -EDTA through the intestinal wall. It is also possible that ^{51}Cr -EDTA had accumulated in some cell phase (*e.g.* RES, compare liver and spleen) in the preparation.

Patients and many experimental animals with serious uraemia often lose considerable amounts of water and electrolytes by vomiting and diarrhoea, this was not the case in any of the animals in the present study.

Apart from a larger PV in the 12 hr-series, the variables studied did not differ significantly from the control values. Numerically, however, the weight and the water content were somewhat smaller in the 12 hr-series than in the controls. This may perhaps be explained by the fact that the gastric contents were nearly significantly larger in the 12 hr-series than in the control series. That no larger differences were found between the 12 hr-series and the controls regarding the parameters studied suggests that nephrectomy had no notable effect on intestinal electrolyte-fluid distribution during the first 12 hrs after nephrectomy.

Autopsy revealed no gross evidence of enterocolitis. Microscopic evidence might, however, have been demonstrable during the later period after nephrectomy. Microscopic changes of enterocolitis in the form of oedema, polymorphonuclear infiltration, haemorrhages and necrosis have been found in dogs (Orbinson et al. 1952) and in rats (Churg & Paterson 1963) some days after nephrectomy. Further, McDermott et al. (1971) demonstrated that within 24 hrs acute renal failure was followed by a clearly reduced renewal rate of mucosal cells in the jejunum in mice. This may

contribute to development of uraemic enteritis and an increased permeability of the mucosal barrier.

During the 12-84 hr period after nephrectomy the weight, the water, FFS and Na and K content of

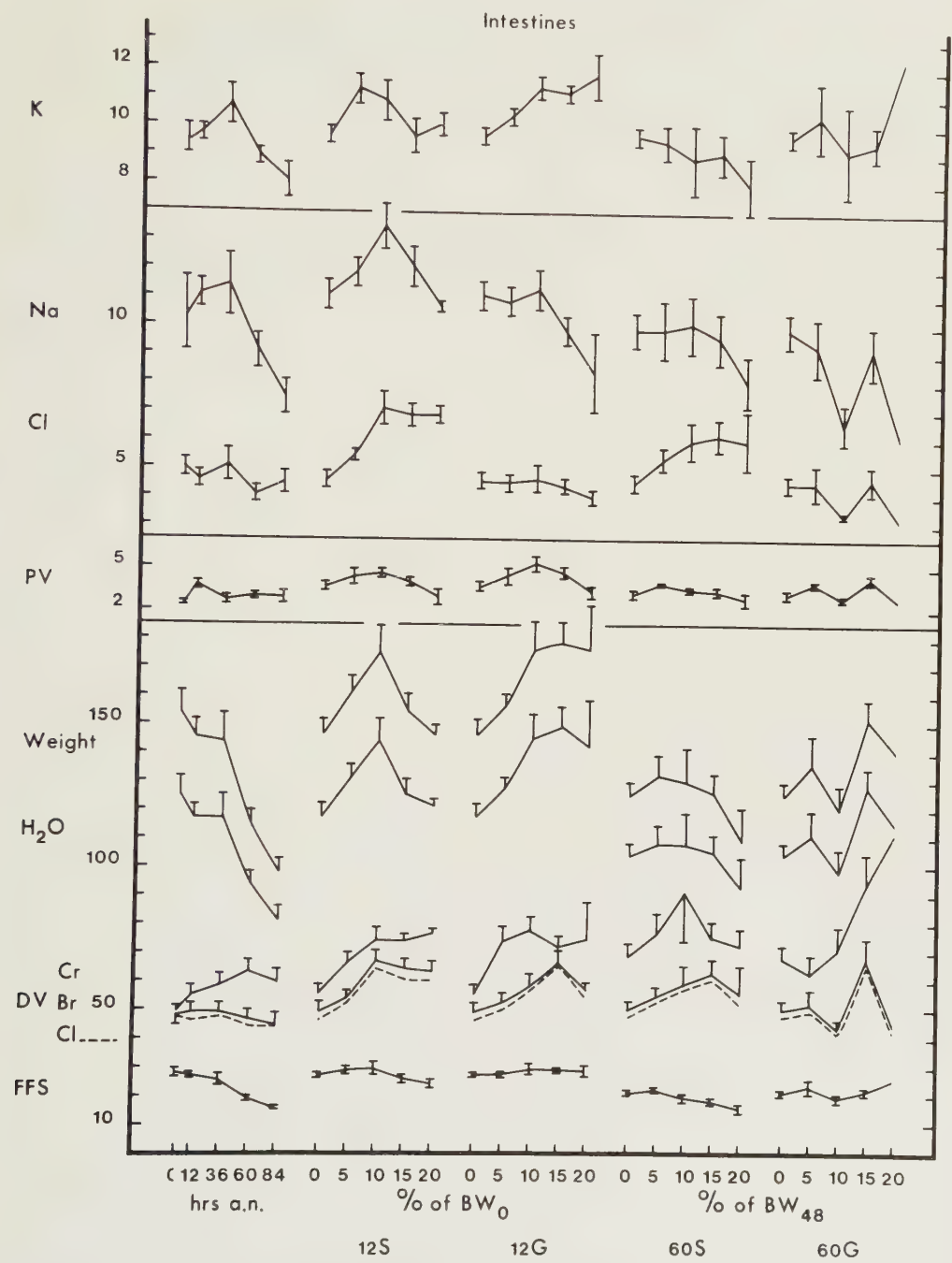


FIG. 10. Effect of nephrectomy and nephrectomy plus overhydration on the intestinal preparation variables determined (g, ml or mEq/kg BW₀ and BW₄₈). For further explanation, see fig. 1.

the intestinal preparation decreased while the Cl content remained unchanged. DV^{Cl} , DV^{Br} and DV^{Cr} did not change, while DV^{Cr} increased hyperbolically. As is clear from the figure reduction of the first mentioned variables was not quite linear. The weight, the water and FFS content were, for example, unchanged during the 12–36 hr period after nephrectomy and afterwards fell almost linearly by about 24 g, 18 ml and 4.9 g/kg $BW_0/24$ hrs, respectively. These events might be explained by the observation that the gastric contents decreased by about 21 g/kg BW_0 during the 12–36 hr period and afterwards fell by only about 5 g during the rest of the period studied. The rate of water and FFS loss from the intestinal preparation seemed thus to be of the same magnitude during the entire 12–84 hr period.

Aach et al. (1957) studied the changes in weight, water-, Na and Cl content of the gastrointestinal tract in experiments on fasting, nephrectomised rats 24 and 48 hrs after nephrectomy. The animals had free access to water. The weight did not change, the water content tended to increase, the Na content diminished and the Cl content of the gastrointestinal tract increased considerably. In the present study the gastric Cl content was not estimated, but like the DV^{Br} of the gastric contents, it undoubtedly decreased during the period studied after nephrectomy. It is at present not possible to say why the Cl content of the gastro-intestinal preparation increased after nephrectomy in the study of Aach et al. (1957), but remained unchanged or diminished in the present investigation. That DV^{Cr} expanded while DV^{Cl} and DV^{Br} were unchanged may be explained in several ways. Uraemic enterocolitis might have resulted in an increased passage of ^{51}Cr -EDTA into cells and/or into the gastrointestinal lumen (compare Stomach and Gastric contents). The true extracellular volume might have increased as a part of a generalised increase of the extracellular volume and/or as a consequence of changes of uraemic enterocolitis (see Stomach). That DV^{Cl} and DV^{Br} did not increase with the DV^{Cr} might have been due to a gradual decrease of the intraluminal amount of these anions.

12S and 60S. As is apparent from the figure, the weight, the water and Na content of the intestinal preparation in the 12S-series increased to reach a high maximum at 10% overhydration, after which they returned to original levels. The amount of FFS in-

creased also hyperbolically to reach a maximum at 10% overhydration, but this change was less marked. In the 60S-series no remarkable changes were found in the weight, the water or Na content. In this last-mentioned series, however, the amount of FFS diminished significantly. The K content was unchanged, while the Cl-content increased hyperbolically in both series.

DV^{Cl} , DV^{Br} and DV^{Cr} increased largely in parallel in the 12S-series. In the 60S-series DV^{Br} increased nearly significantly, DV^{Cl} and DV^{Cr} only numerically. No significant differences were found between 12S and 60S-series regarding the magnitude of the changes recorded.

No explanation for the observed relationship between the degree of overhydration and the weight, the water and the Na content of the intestinal preparation in the 12S-series could be offered.

If any notably changes of enterocolitis had existed in the 60S-series, one would have expected, as in the stomach, a much stronger increase of DV^{Cl} , DV^{Br} and DV^{Cr} than what was found.

12G and 60G. The amount of water in the intestinal preparation increased markedly and hyperbolically in the 12G-series, in contrast with the 60G-series, where the increase noted was only numerical. DV^{Cl} , DV^{Br} and DV^{Cr} increased in the 12G-series. As is apparent from the figure, the expansion of DV^{Cr} was not quite parallel to that of DV^{Cl} and DV^{Br} . In the 60G-series DV^{Cr} increased hypobolically, while DV^{Cl} and DV^{Br} did not change in any particular way. The K content increased in the 12G-series, while the Na-content decreased to a corresponding extent. The Na content tended to decrease also in the 60G-series, but without any corresponding increase in the K content. The Cl content and the amount of FFS of the intestinal preparation remained unchanged in both series.

No significant differences were found between the 12G and 60G-series regarding the magnitude of the changes recorded.

That the amount of water seemed to increase more in the 12G-series than in the 60G-series may be ascribed, above all, to the fact that the animals in the 12G-series had a larger amount of intraluminal contents which might have osmotically contributed to the binding of water. Only a minor part of the increase in the K content in the 12G-series could be ascribed to

an increase in the extracellular amount of K. An increase must thus have occurred in the intracellular and/or intraluminal amount of K.

The discrepancy between the changes in DV^{Cr} and those of DV^{Cl} and DV^{Br} illustrates that ^{51}Cr -EDTA did not measure exactly the same water phases in the intestinal preparation as did Cl and ^{82}Br .

LIVER (Fig. 11)

C-12 hrs and 12-84 hrs. As the liver is rich in blood its electrolyte-fluid content must depend largely on the volume of blood in it, the haematocrit and the

red cell electrolyte concentrations. But since the vascular bed of the liver is relatively "open" it is difficult to get a really representative amount of blood in the organ when it is removed at autopsy for analysis.

The liver tissue has two non-cellular fluid phases, the true extracellular phase and the bile system, with different electrolyte concentrations. It is therefore impossible to estimate the extracellular space from the concentration of the extracellular markers used.

In the present investigation the ^{51}Cr -EDTA space of the liver was 62%, i.e. ^{51}Cr -EDTA must have penetrated into or have been taken up by some cellular

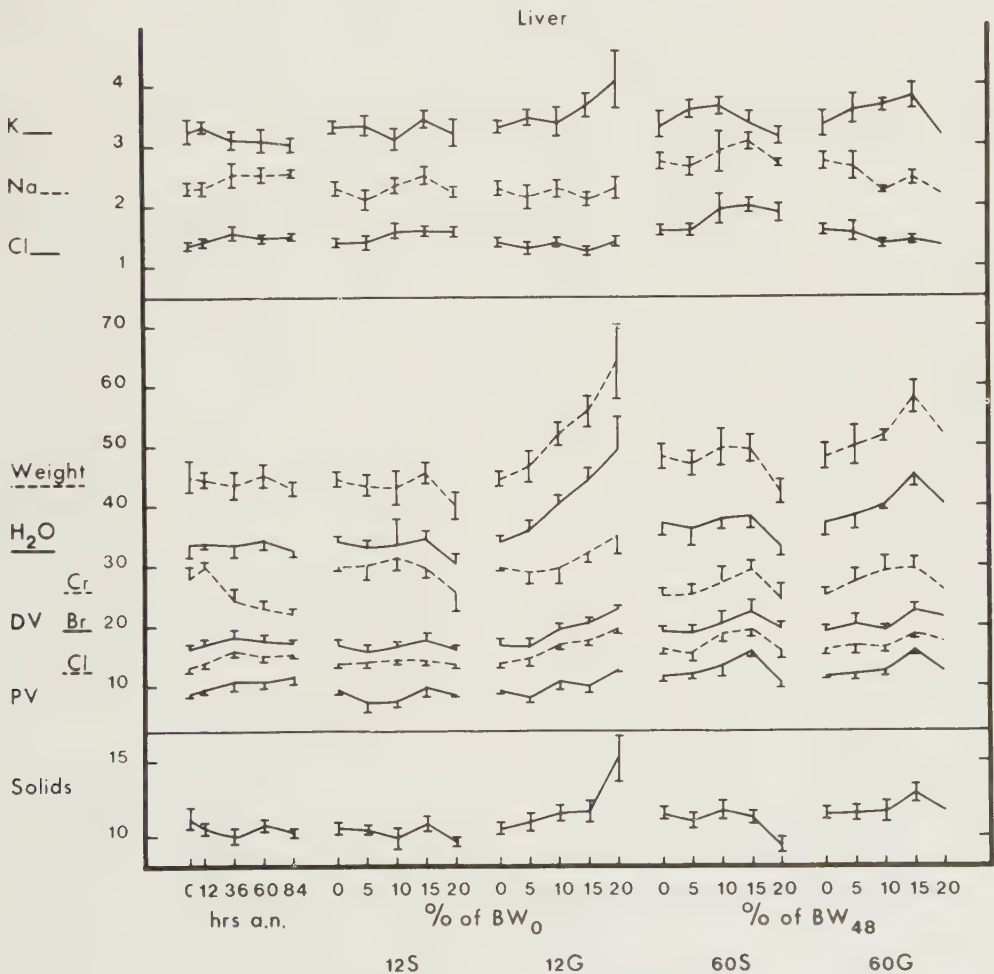


FIG. 11. Effect of nephrectomy and nephrectomy plus overhydration on the liver variables determined (g, ml or mEq/kg BW_0 and BW_{48}). For further explanation, see fig. 1.

phase. It was not due to a high bile ^{51}Cr -EDTA concentration since the latter was found to be the same as in plasma in a pilot study (unpublished personal observations). The DV^{Br} was somewhat larger than DV^{Cl} throughout. The above finding can hardly be due entirely to technical errors.

No differences were found between the controls and the animals 12 hrs after nephrectomy regarding the variables studied.

The only significant change observed during the 12–84 hr period after nephrectomy was a highly significant decrease in the DV^{Cr} of the liver, from 30.1 ± 1.5 ml to 21.9 ± 0.9 ml/kg BW_0 . The PV, DV^{Cl} , DV^{Br} , the Na and Cl content tended to increase and the K content to decrease, while the weight and the water content persisted unchanged.

The decrease in the DV^{Cr} of the liver after nephrectomy might be ascribed to an active accumulation of ^{51}Cr -EDTA in the liver cells and/or in the reticuloendothelial cells of the liver and an inhibition of this process by the increasing uraemic intoxication. It was not possible to decide from the numerical changes in the other electrolyte-fluid variables whether any redistribution of electrolytes and fluid occurred between various fluid phases of the liver.

Aach et al. (1957) observed that the liver weight and water content decreased during the first 48 hrs after nephrectomy in fasting rats with free access to water. Gessler & Caliebe (1960) found that the water and the K content were significantly, and the Na content nearly significantly, larger in rats nephrectomised 33 hrs previously and allowed water and food *ad lib*. These findings could not be confirmed in the present study in rabbits deprived of food and water after nephrectomy.

12S and 60S. Apart from a nearly significant and a significant increase in the Cl content of the liver in the 12S and 60S-series, respectively, no significant changes were found in the variables in the two saline overhydrated series. The PV of the liver increased to a maximum at 15% overhydration and afterwards returned to original level in the 60S-series, which might have reflected changes observed in the CVP in this series. The other fluid variables and the Na content varied with the PV of the liver in the 60S-series. Though the CVP curve of the 12S-series resembled that in the 60S-series, no such changes could be found in the 12S-series.

As expected, saline overhydration produced no dramatic changes in the liver variables studied.

12G and 60G. In the 12G-series the weight of the liver increased considerably. One fifth of this increase could be ascribed to a nearly significant increase of the amount of solids and the rest to a significant increase in the water content. The DV^{Cl} and DV^{Br} increased significantly, but only by half as much as the water. The Na and Cl content remained unchanged, while the K content tended to increase.

In the 60G-series the weight of the liver also increased significantly, but somewhat less than in the 12G-series. About 60 percent of this increase was due to a nearly significant increase of the water content and the rest to a numerical increase in the amount of solids. Further, the DV^{Br} increased nearly significantly parallel to a numerical increase of DV^{Cl} , DV^{Cr} and PV. The Na and Cl content tended to decrease, while the K content, as in the 12G-series, tended to increase.

There were no significant differences between the 12G and 60G-series regarding the magnitude of the changes observed. The numerical increases of the water content was, however, twice as large in the former series.

As expected, glucose overhydration caused intracellular oedema of the liver. That DV^{Cl} and DV^{Br} appeared to increase more in the 12G-series than in the 12S-series may have been due to the fact that the fall in the concentration of Cl and ^{82}Br in one or the other of the liver phases was not parallel to that of the extracellular concentration of these anions. That the K content of the liver tended to increase in the two glucose overhydrated series was possibly a consequence of a glucose uptake by the liver cells, an assumption which gains force from the fact that the amount of solids seemed to increase in the two series. The quotient between the increase in liver cell K and that in the solids was 0.65 in the 12G-series and 0.53 mEq/g in the 60G-series, values agreeing well with the observation that the intracellular K content increase by about 0.45 mEq/g new-formed glycogen (Bergström et al. 1967). Why the water content of the liver appeared to increase more in the 12G than in the 60G-series could not be explained.

Wasterlain & Posner (1968) injected vasopressin into rats and then overhydrated them with distilled water. This treatment resulted in a significant increase

of the water content of the liver and a numerical increase and decrease, respectively, of the Na and K content. In the evaluation of these results the extrarenal effects of vasopressin must be taken into account.

SPLEEN

C-12 hrs and 12-84 hrs. No differences were found between the 12 hr-series and the controls regarding the variables studied.

During the 12-84 hr period after nephrectomy the weight and the DV^{Br} of the spleen fell significantly and the DV^{Cr} nearly significantly. The PV remained unchanged. The weight decreased less than DV^{Br} and DV^{Cr} .

The interstitial volume of the spleen thus decreased, while the intracellular volume and/or the amount of solids in the spleen increased. An increase in the amount of solids might perhaps have been due to increased haemolysis.

Aach et al. (1957) found that the water content of the spleen diminished in rats deprived of food after nephrectomy, which appears to be compatible with the findings in the present study.

It should be observed that DV^{Cr} was equally large as DV^{Br} though the spleen must have contained a significant amount of red cells with a high ^{82}Br concentration. This finding suggests that ^{51}Cr -EDTA accumulates in some phase or is bound to some extracellular structure in the spleen (see Liver and Intestinal preparation).

12S and 60S and 12G and 60G. Neither saline nor glucose overhydration caused any significant change in the variables determined in the spleen. The range of the values was, however, large.

LUNGS (Fig. 12)

C-12 hrs. No radiographic changes could be demonstrated in the lungs in the 12 hr-series or in the controls. Autopsy revealed small dark-red spots on the surfaces of the lungs in 2 of the 17 animals in the 12 hr-series. No gross changes were seen on the surface of the lungs in any of the controls. At microscopic examination one of the 9 controls and 9 of the 17 animals in the 12 hr-series were classed as (+). In none of the other animals in these two series were protein deposits found in the alveoli.

The weight and the electrolyte-fluid composition of the lungs vary with the way in which the animal is killed and autopsied (see Lindquist 1964). The findings in the present investigation are not strictly comparable with those reported by earlier investigators owing to differences in the experimental design.

The DV^{Br} was clearly larger than the DV^{Cl} of the lungs throughout in the present study. The DV^{Cr} was somewhat less than DV^{Cl} , but DV^{Cr} could hardly have measured the true extracellular space, since DV^{Cl} was smaller than DV^{Cr} when the Cl content of the red cell volume of the lungs was taken into account.

The weight, the water content, the DV^{Cl} , DV^{Br} and DV^{Cr} of the lungs were nearly significantly, and the Na and Cl content significantly, smaller in the 12 hr-series than in the controls. Otherwise no significant differences were found between the two series.

The interstitial volume of the lungs appeared, thus, to be smaller in the 12 hr-series than in the controls, though half of the animals in the former series showed morphologic signs of a certain degree of intra-alveolar oedema. The reduction of the interstitial volume might be explained by some effect of nephrectomy on the pulmonary circulation (see the parallel changes in the peripheral circulation).

12-84 hrs. Seven animals (2 in the 12 hr, 2 in the 36 hr, and 3 in the 60 hr-series) showed solitary dark-red spots on the surfaces of the lungs, usually situated basally or near the hilus. No correlation was found between these findings and the other pulmonary variables studied. In none of the animals were any radiographic changes observed.

The frequency of animals classed as (+) and + regarding the occurrence of alveoli filled with protein precipitates, increased with the interval after nephrectomy (see the first table in Appendix). No animal was classed as ++ or +++.

It is clear from the Fig. 12 that the lung weight, water, Na and Cl content and DV^{Cl} , DV^{Br} and DV^{Cr} increased hyperbolically to reach the level in the controls. The amount of solids increased nearly significantly, while the K content tended, if anything, to decrease, and the PV of the lungs remained unchanged.

The changes observed may reasonably be ascribed to a development of uraemic pneumonitis with an increase of the interstitial space, alveolar oedema and invasion of white blood cells (the increase of the amount

of solids). The tendency of the K content of the lungs to decrease despite the increase in extracellular K concentration and in the extracellular volume may be explained by the decrease in the red cell K concentration and in the haematocrit.

Lindqvist (1964) observed the following pulmonary changes with time in rabbits after bilateral ureteric

ligation: slight radiographic changes in 3% within 3 days and an increasing frequency of animals with red dots on the lung surfaces. In contrast with the findings in the present study, he did not observe increasing intra-alveolar oedema or any changes in the weight of the lungs. These discrepancies may be due to nephrectomy not having the same effect on, among

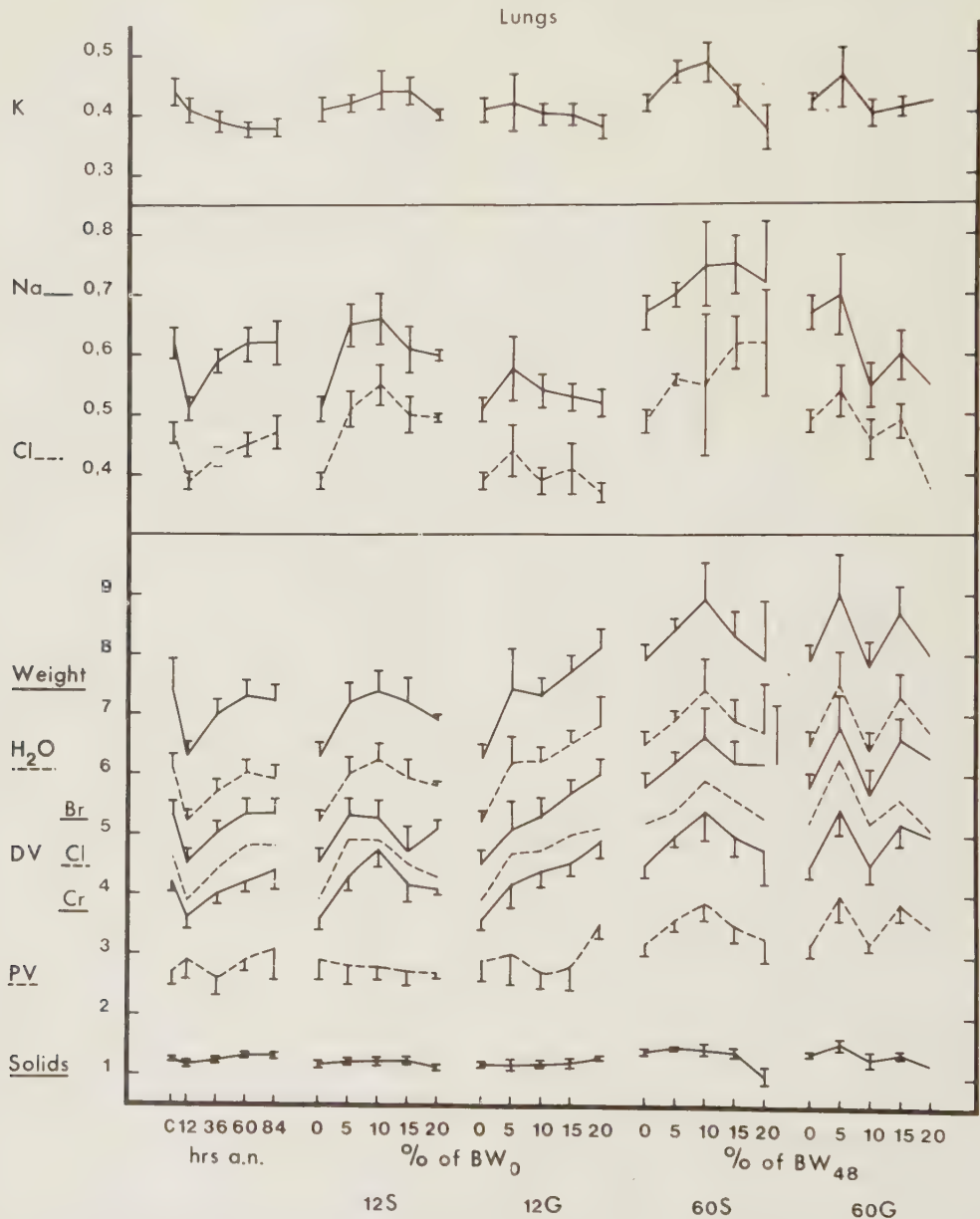


FIG. 12. Effect of nephrectomy and nephrectomy plus overhydration on the lung variables determined (g, ml or mEq/kg BW₀ and BW₄₈). For further explanation, see fig. 1.

other things, the pulmonary circulation as bilateral ureteric ligation and second, to differences in the way the animals were killed in the two studies. The increasing frequency of alveoli filled with protein precipitate may be explained *inter alia* by changes in the surfactant system of the alveoli (Ajewski et al. 1970).

12S and 60S. No radiographic pulmonary changes could be noted in the 12S and the 60S-series. Autopsy revealed small red dots on the lung surfaces in 12 (31%) of the 39 overhydrated animals in the 12S-series and in 8 (33%) of 25 overhydrated animals in the 60S-series. There was no correlation between the frequency of animals with red dots and the degree of overhydration. There was an apparent correlation between the degree of overhydration and occurrence of alveoli filled with protein precipitate (see the first table in Appendix). This correlation was most marked in the 60S-series, in which 5 of the overhydrated animals were classed as ++. In the 12S-series no animal was classed as ++ or +++. In the 12S-series the lung weight, Na and Cl content and all of the fluid variables, with the exception of PV, increased hyperbolically. In the 60S-series all the fluid variables, including PV as well as the K content, increased to reach a maximum at 10% overhydration and afterwards gradually returned to their control levels. The Na and Cl content increased in this series nearly significantly and significantly, respectively.

In the 12S-series, then, the interstitial volume of the lungs recovered the values of the control series and a slight increase occurred in the amount of water within the alveoli.

In the 60S-series no increase of the interstitial space of the lungs was observed with certainty, but also in this series the water amount within the alveoli increased somewhat as judged from the microscopical findings.

Lindqvist (1964) overhydrated rabbits to 15% of the bodyweight with Ringer solution at a varying interval after bilateral ureteric ligation and found the following pulmonary changes: slight radiographic signs of pulmonary oedema in some animals with high degree of uraemia, an increased frequency of red spots on the lung surfaces, especially in the animals with a high degree of uraemia and an increased lung water content. On the other hand, he found no increase in the frequency of alveoli filled with protein precipitate or of the weight of the lungs. The difference between Lindqvist's findings regarding the frequency of alveoli

filled with protein precipitate and those made in the present investigation may, as pointed out previously, be ascribed to differences in the experimental conditions used.

12G and 60G. As in the 12S and 60S-series no radiographic pulmonary changes could be demonstrated in the 12G and 60G-series. At post mortem 8 (21%) of the 39 overhydrated animals in the 12G-series and 4 (17%) of the 23 overhydrated animals in the 60G-series showed small red spots on the lung surfaces. In the 12G-series, but not in the 60G-series, a correlation was found between the degree of overhydration and the frequency of alveoli filled with protein precipitate (see the first table in Appendix).

In the 12G-series the weight of the lungs, the water content, DV^{Cl} , DV^{Br} and DV^{Cr} increased significantly and linearly, while the PV remained unchanged. No changes were found in the Na, K or Cl content in this series. In the 60G-series weight of the lungs and the fluid variables including PV showed no clear change. In this series the Na and the Cl content diminished nearly significantly, while the K content, as in the 12G-series, persisted unchanged.

The observed increase in the water content and DV^{Cl} , DV^{Br} and DV^{Cr} in the 12G-series probably reflected an increase of the interstitial space of the lungs and some increase in the amount of fluid in the alveoli. In contrast with the 12G-series, the 60G-series showed no increase of the interstitial or the intraalveolar fluid (see the 12S and the 60S-series).

Lindqvist (1964) overhydrated rabbits to 15% of the bodyweight with 5% glucose solution 48 hrs after bilateral ureteric ligation and observed no significant pulmonary changes.

Thus, neither hypo-osmotic nor iso-osmotic overhydration appears to produce any notable pulmonary oedema in nephrectomised rabbits.

BRAIN (Fig. 13)

C-12 hrs and 12-84 hrs. Owing to the complexity of the electrolyte-fluid distribution in the brain the changes observed in the variables studied are difficult to interpret. The values found are nevertheless given to contribute to a more complete picture of the electrolyte-water movements between different tissues under the experimental conditions used.

The values found for the water, Na, K and Cl content of the brain in the controls agreed well with

those given by other investigators for rabbits (Ames & Nesbitt 1958, Van Harreveld 1961, Bradbury et al. 1968).

Since Br, like I and SCN, is actively excreted from the cerebrospinal fluid (Bito et al. 1966, Streicher et al. 1964) the DV_m^{Br} of the brain is dependent on the

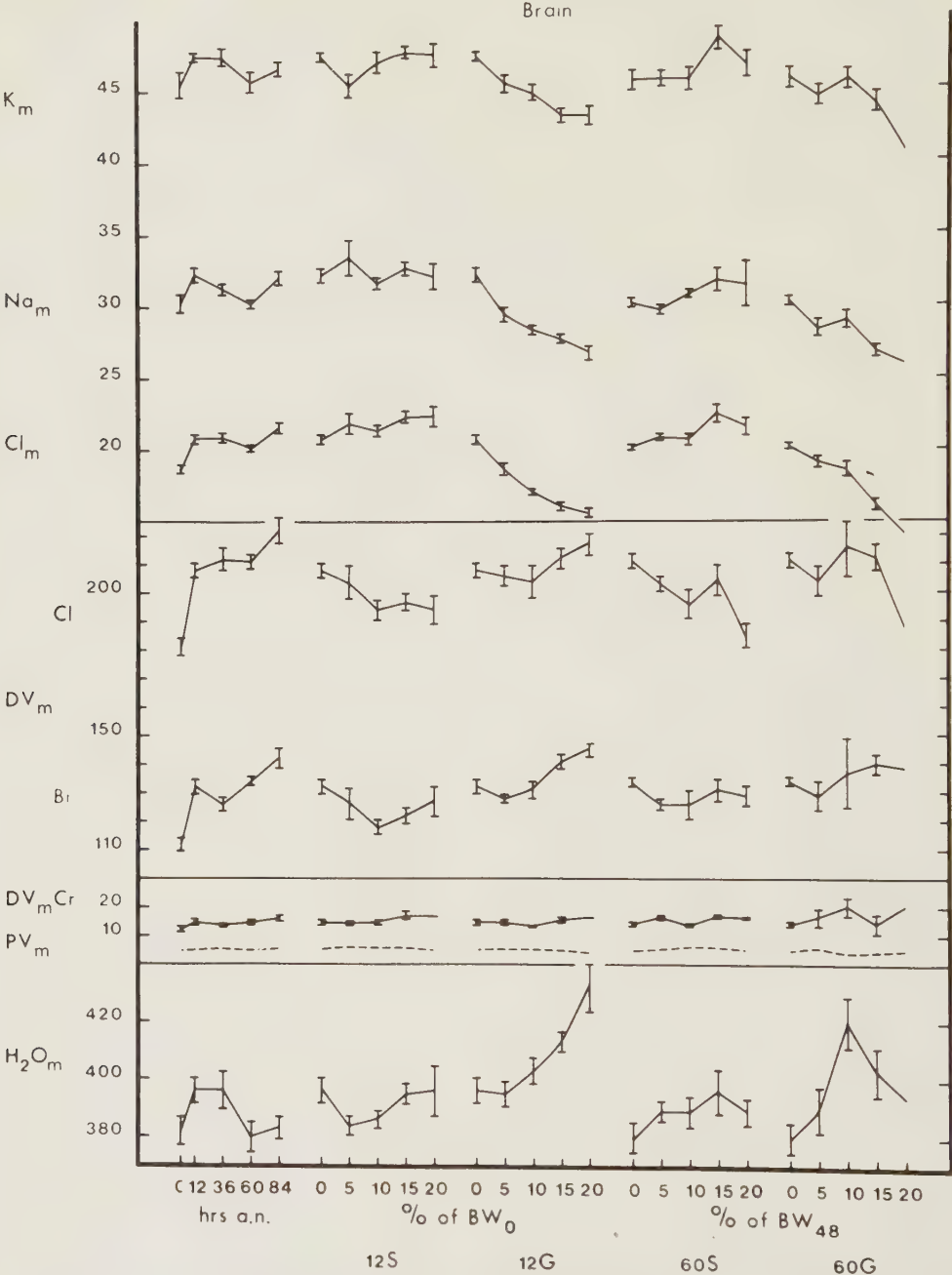


FIG. 13. Effect of nephrectomy and nephrectomy plus overhydration on the brain variables determined (ml or mEq/100 g solids). For further explanation, see fig. 1.

plasma Br concentration, at least in pharmacological concentrations. Whether this holds also for trace concentrations of Br used in the present study is not known. Caution must therefore be exercised in the evaluation of the DV_m^{Br} -values in the present study.

In the control series the ^{51}Cr -EDTA space of the brain was $2.5 \pm 0.16\%$ of the wet tissue, a figure of the same magnitude as that given in the literature for the inulin and the sucrose space of the brain (see Van Harreveld 1966) which suggests that ^{51}Cr -EDTA does not pass through the blood-brain-barrier to any appreciable extent. That ^{51}Cr -EDTA, like other EDTA-chelates, is excluded by the blood-brain-barrier, has also been observed by Lökken (1969).

The DV_m^{Cl} , DV_m^{Br} and Cl_m were significantly, the Na_m and K_m nearly significantly, and the H_2O_m numerically larger in the 12 hr-series than in the controls.

During the 12–84 hr period after nephrectomy the DV_m^{Cl} and DV_m^{Br} continued to increase significantly, but at a much lower rate than during the first 12 hrs after nephrectomy. The H_2O_m , Na_m and K_m tended to decrease, while the Cl_m remained unchanged during the 12–84 hr period. The DV_m^{Cr} and PV_m persisted unchanged throughout the period studied after nephrectomy.

No explanation can be offered for the initial accumulation of water, Na, K and Cl found in the brain tissue. An increase of the Na and K content after nephrectomy has been reported earlier in rats (Fishman & Raskin 1967, Fishman 1970), but in those investigations the water and the Cl content decreased. This latter discrepancy may, however, be explained by differences in the experimental conditions and/or species. An increased blood-brain permeability to sucrose and inulin (Fishman, 1970) and an increased ratio between the concentration of Br in the cerebrospinal fluid and that in plasma have been observed in uraemia (Freeman et al. 1962). The latter observation was in agreement with the finding in the present study that the DV_m^{Br} increased after nephrectomy. That the DV_m^{Cr} did not increase suggests that the blood-brain barrier was largely intact during the period studied. That the DV_m^{Cl} increased during the 12–84 hr period after nephrectomy was due mainly to the decreasing plasma Cl concentration without associated reduction of the Cl_m of the brain.

12S and 60S. The DV_m^{Cl} decreased in both the 12S and the 60S-series. The decrease was of the same relative magnitude in the two series. The DV_m^{Br} decreased nearly significantly in the 12S and numerically in the 60S-series. The DV_m^{Cr} increased numerically in the 12S-series and nearly significantly in the 60S-series. The H_2O_m tended to decrease hypobolically in the 12S-series, but tended to increase in the 60S-series.

In the 12S-series the Cl_m tended to increase, while the Na_m and K_m persisted unchanged. In the 60S-series the Cl_m increased significantly and the Na_m and K_m nearly significantly.

No significant differences in the b-values were found between the 12S and the 60S-series. The observed decrease in the DV_m^{Cl} can hardly be ascribed to a reduction of the extracellular volume of the brain, but rather to the fact that the Cl content of the brain increased relatively less than the plasma Cl concentration. It is not known whether this was a manifestation of a transient disequilibrium.

That no significant change of the water content of the brain could be observed in the two saline overhydrated series is in agreement with the observations of Gerschenfeld et al. (1959) and DeRorbetis & Gerschenfeld (1961).

That K_m increased in the 60S-series, while the plasma K concentration decreased in that series suggests that the amount of intracellular K increased in the brain.

12G and 60G. In the glucose overhydrated series the H_2O_m increased, while the Na_m , K_m and Cl_m decreased. The DV_m^{Br} increased significantly in the 12G-series and numerically in the 60G-series. The DV_m^{Cl} and DV_m^{Cr} did not change in any particular way in either of the series. The PV_m was unchanged.

No significant differences in the b-values were found between the 12G and 60G-series.

The findings that the Na_m , K_m and Cl_m decreased, while the H_2O_m increased at hypotonic overhydration corroborate the observations by other authors (Dodge et al. 1960, Stern & Coxon 1964, Wasterlain & Posner 1968). If the brain is allowed to expand without increase in pressure, no K is lost (Van Harreveld et al. 1966).

That the DV_m^{Br} increased in the 12G-series and tended to increase in the 60G-series may have been due to

an increased permeability to ^{82}Br and/or a negative effect on the active Br excretion from the cerebrospinal fluid. But the cerebral oedema did not appear to have produced any severe impairment of the blood-brain barrier, as the DV_m^{Cr} did not increase.

CARDIAC MUSCLE (Fig. 14)

C-12 hrs and 12-84 hrs. Johnson & Simmonds (1962) found that the histological extracellular space, the T-tubuli system not included, was $26.4 \pm 1.9\%$ in the ventricular muscle in rabbits. This value agrees well with the ^{51}Cr -EDTA-space found in the present investigation $26.0 \pm 1.1\%$. The sucrose-space and SCN-space in the Johnson & Simmonds study were 39.6 ± 0.75 and $55 \pm 3.3\%$, respectively, values which were larger than the C1 and Br-space in the present study (30.9 ± 0.8 and 32.1 ± 0.7 , respectively). Otherwise the values for the variables studied in the control series agreed with those reported earlier for the heart and cardiac muscle in the rabbit (Manery & Hastings 1939, Manery & Bale 1941, Hitching et al. 1942, Aikawa 1950, Gross & Smith 1958).

The weight, the water, FFS, K and C1 content of the heart increased significantly throughout the studied period after nephrectomy, while the Na content was unchanged.

H_2O_m , $\text{H}_2\text{O}_i^{\text{Cr}}$ and $\text{H}_2\text{O}_e^{\text{Cr}}$ did not change significantly. K_i and $[\text{K}]_i$ increased initially after nephrectomy and then decreased almost significantly and numerically, respectively. Na_i and $[\text{Na}]_i$ appeared to decrease continuously. Cl_i and $[\text{Cl}]_i$ tended to increase hyperbolically. The ratio $[\text{K}]_i / [\text{K}]_e$ decreased significantly and the ratios $[\text{Cl}]_e / [\text{Cl}]_i$ and $[\text{Br}]_e / [\text{Br}]_i$ tended to decrease during the period studied, while the ratio $[\text{Na}]_e / [\text{Na}]_i$ was unchanged.

The amount of water and solids in the heart thus increased continuously after nephrectomy. The amount of water increased in both the intra and the extracellular space since the ratio between $\text{H}_2\text{O}_i^{\text{Cr}}$ and $\text{H}_2\text{O}_e^{\text{Cr}}$ was unchanged. The intracellular space of the heart initially accumulated K and in the later course lost part of its K-excess. The intracellular Na content and concentration tended to decrease while those of the C1 appeared to increase. The changes recorded in the electrolyte-fluid distribution in the heart differed in several respects from those in the skeletal muscle.

That $[\text{Na}]_i$ decreased might have been due to a decrease of the extracellular Na and an increase of the extracellular K concentration. As in the skeletal muscle, the glycogen content of the cardiac muscle may have decreased and thereby also the intracellular K-binding capacity. The increasing acidosis may, of course, have had a negative effect on the intracellular K content. The changes found suggest that the uraemia had no appreciable depressive effect on the Na-K-pump in the cardiac muscle.

That the amount of FFS in the heart increased during the period studied after nephrectomy may have been due to "uraemic" myocarditis with haemorrhages, focal necrosis accompanied by inflammatory infiltration and calcification (Schreiner & Maher 1961, Orbinson et al. 1962, Churg & Paterson 1963) and partly by cardiac hypertrophy, secondary to the observed renoprival hypertension (Hall et al. 1953, Houck 1954).

Aach et al. (1957) noticed no change in H_2O_m of the cardiac muscle after nephrectomy in fasting rats with free access to water. Ledingham (1954) observed that Na_i and $[\text{Na}]_i$ were decreased in cardiac muscle, while K_i , $[\text{K}]_i$ and H_2O_i were increased with inulin as an extracellular marker 3 days after nephrectomy in rats with free access to electrolyte-free food and distilled water or 0.5% NaCl. Except for the H_2O_i increase these findings agreed well with those in the present study.

Gessler & Caliebe (1961) found that H_2O_m , Na_m and K_m of cardiac muscle were increased in rats with free access to food and water 33 hrs after nephrectomy; in other words, findings not compatible with those in the present study.

Fishman & Raskin (1967) found that Na_m and Cl_m were increased, while K_m and H_2O_m were unchanged in cardiac muscle 48 hrs after nephrectomy in rats with free access to 5% glucose solution. There are thus certain differences between their findings and those made in the present study. The Cl_m decrease observed by them may correspond to the Cl_m decrease found in the two glucose overhydrated series in the present investigation (see below), since the plasma C1 concentration was considerably reduced in the study of Fishman and Raskin (1967).

12S and 60S. The weight, the water, Na and K content of the heart were unchanged in the two saline

overhydrated series, while the Cl content increased in both series. $H_2O_e^{Cr}$ increased nearly significantly and significantly, respectively in the 12S and the 60S-series. $H_2O_e^{Cr}$ did not vary with certainty in any of the series. The K_i increased nearly significantly, while the $[K]_i$ was

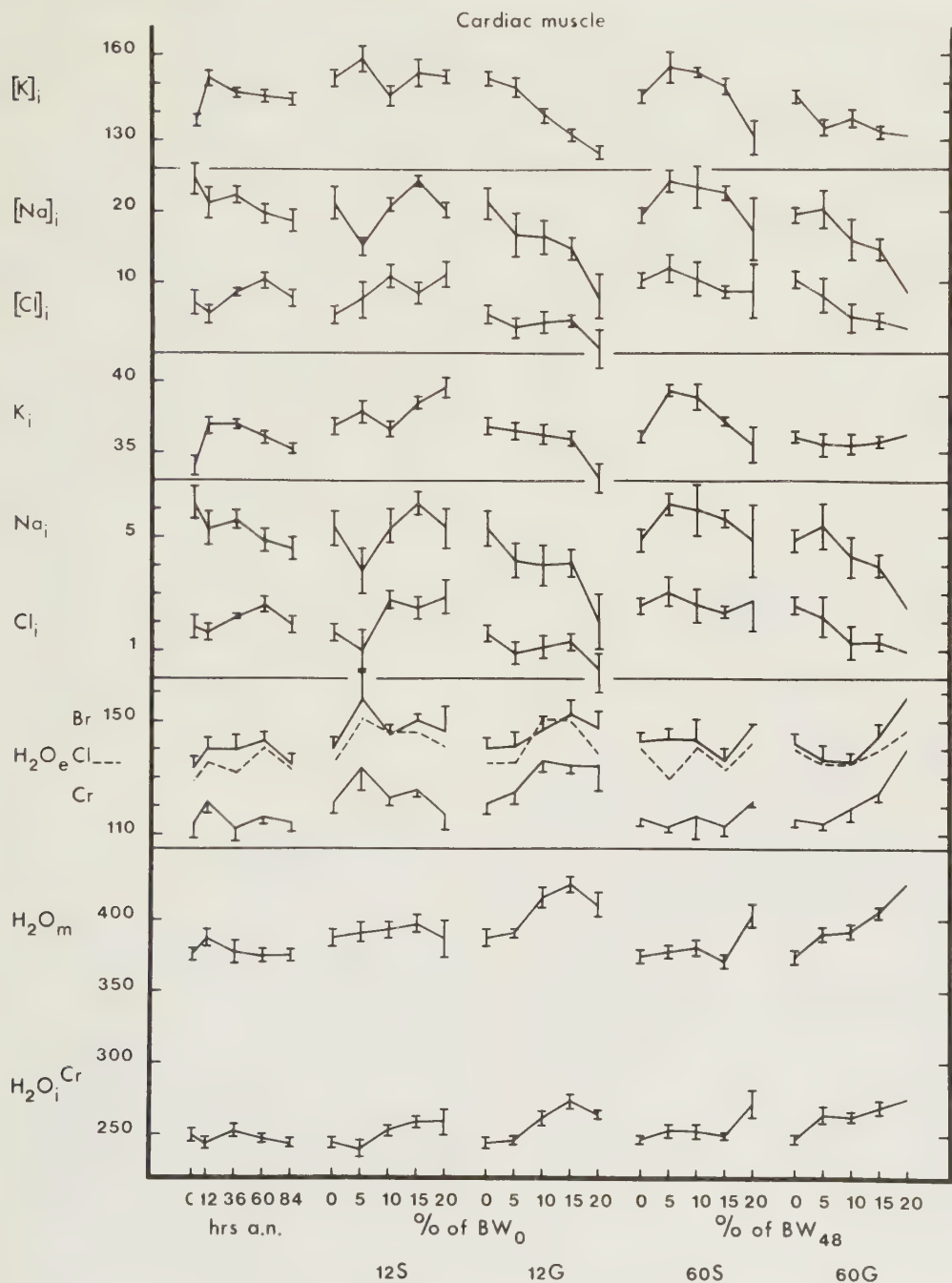


FIG. 14. Effect of nephrectomy and nephrectomy plus overhydration on the cardiac muscle variables determined (ml or mEq/100 g FFS). For further explanation, see fig. 1.

unchanged in the 12S-series. In the 60S-series K_i and $[K]_i$ increased hyperbolically. This appeared to be the case also for Na_i and $[Na]_i$ in the same series. In the 12S-series the last mentioned variables showed no clear change. Cl_i and $[Cl]_i$ increased nearly significantly in the 12S-series, but was unchanged in the 60S-series. In the 60S-series the ratio $[K]_i / [K]_e$ increased significantly. Otherwise no significant changes were found in the membrane quotients for the electrolytes determined.

There were no significant differences between 12S and 60S-series regarding the b-values.

A possible explanation for the increase in $H_2O_i^{Cr}$ on saline hydration is that parts of the T-tubuli system not equilibrated with ^{51}Cr -EDTA increased in volume. Sperelakis & Rubio (1971) found that the T-tubuli in cardiac muscle became markedly swollen and exceedingly prominent in hypertonic solution.

12G and 60G. The weight and the water content of the heart tended to increase in the two glucose overhydrated series, while the Cl content decreased significantly in both and the Na content decreased numerically respectively significantly in the 12G and 60G-series. The amount of FFS was unchanged.

$H_2O_i^{Cr}$ and $H_2O_e^{Cr}$ increased in both the series. The increases were of the same magnitude in both series. The $H_2O_e^{Cr}$ increase was significantly larger than in the corresponding saline overhydrated series. K_i was unchanged while $[K]_i$ and $[Na]_i$ decreased significantly and Na_i decreased nearly significantly in both series. Cl_i and $[Cl]_i$ decreased significantly in the 60G-series but only numerically in the 12G-series. The ratio $[K]_i / [K]_e$ in the 60G-series as well as in the 60S-series tended to increase. In both the 12G and 60G-series the ratio $[Br]_e / [Br]_i$ increased while the ratio $[Cl]_e / [Cl]_i$ only increased in the 60G-series. The membrane quotient for Na did not change significantly in any of the two series.

There were no significant differences between the 12G and the 60G-series concerning the magnitude of the changes found.

That $H_2O_e^{Cr}$ increased more on glucose than on saline overhydration may perhaps be due to an increased cellular permeability to ^{51}Cr -EDTA, an increase in the volume of the T-tubules system, a more complete equilibration of ^{51}Cr -EDTA in this system

and/or an impaired transport of extracellular fluid via the lymph.

In the evaluation of the fluid and electrolyte variables it should be borne in mind that the glycogen content may have increased in the cardiac muscle in the two glucose overhydrated series (see Rebar et al. 1959). Such an increase has no notable effect on K_m and K_i , but can result in underestimation of the other variables. This source of error may, however, not have been so large since no increase was found in the total amount of FFS in the heart.

WHITE AND RED SKELTAL MUSCLE (WM AND RM) (Figs. 15 and 16)

C-12 hrs and 12–84 hrs. It was considered of interest to find out whether the changes in the electrolyte-fluid composition were the same in skeletal muscles with more or less red muscle fibres since they differ somewhat in histological picture, biochemical and electrolyte-fluid composition (Drahota 1960, Beatty et al. 1963, Reis & Wooten 1970). As for the electrolyte-fluid composition Sréter & Woo (1963) found that skeletal muscles containing more red fibres had a larger inulin-space, higher Na and lower K content than those containing fewer red fibres. These findings were corroborated in the study when ^{51}Cr -EDTA was used as an extracellular marker. Reis & Wooten (1970) found that the capillary density was higher in red than in white skeletal muscle, results compatible with the finding in the present study that PV_m was larger in RM than in WM.

Although the literature concerning the normal electrolyte-fluid composition of the mammalian skeletal muscle is voluminous, only relatively few studies have been performed in the rabbit. The electrolyte-fluid composition varies somewhat between mammalian species, muscle groups and ages. It is therefore difficult to compare the results obtained in different series. The H_2O_m , K_m , Na_m and Cl_m values found for the quadriceps femoris muscles in the controls were, however, largely in good agreement with those reported by earlier authors in different muscle groups in the rabbit (Manery & Bale 1941, Gross & Smidt 1958, Bradbury et al. 1968) and in other mammalian species (for ref. see Bergström 1964). $H_2O_e^{Cr}$ was smaller than $H_2O_e^{Cl}$ and $H_2O_e^{Br}$, which were equal. $H_2O_e^{Cr}$ was therefore considered a better mirror of the true H_2O_e and was used throughout in the calculation

of the amount of extracellular water and electrolytes.

In the present study the fat-free solids (FFS) were used as the basis of the reference for water and electrolytes. This reference assumes that the amount of red cells and their electrolyte-fluid content is constant, and that the relation between the amount of connective tissue solids and that of muscle cells does not change. To eliminate some of these sources of error the calculated red cell water and electrolyte values were subtracted from the intracellular values. There might have been some shifts in the relation between the connective tissue and muscle cell solids owing to muscle catabolism and change in glycogen content (Bergström et al. 1965, Bergström & Hultman 1969), but such shifts were assumed to be relatively small under the experimental conditions used.

H_2O_m and $H_2O_i^{Cr}$ increased in both WM and RM hyperbolically with a maximum 36–60 hrs after nephrectomy in the nephrectomised, non-overhydrated animals. The H_2O_e measured with the three reference substances increased initially after nephrectomy and afterwards persisted at a relatively high level.

K_i increased largely parallel to the $H_2O_i^{Cr}$ in both WM and RM. $[K]_i$ increased initially after nephrectomy in RM and afterwards persisted at a somewhat higher level than in the control series. In WM $[K]_i$ did not change after nephrectomy.

Na_i and $[Na]_i$ increased in WM, but remained unchanged in RM. Cl_i and $[Cl]_i$ increased hyperbolically in both RM and WM. The ratios $[K]_i / [K]_e$, $[Cl]_e / [Cl]_i$ and $[Br]_e / [Br]_i$ decreased in both WM and RM. The ratio $[Na]_e / [Na]_i$ decreased in WM but not in RM.

Ledingham (1954) studied the effect of nephrectomy on the electrolyte-fluid distribution in rats with free access to electrolyte-free food and water. He used inulin as a marker for the extracellular water. Three days after nephrectomy Na_i and $[Na]_i$ were decreased, while K_i and $[K]_i$ were unchanged in skeletal muscle. The plasma K concentration was about 8 mEq/l. Though the extracellular volume increased considerably, the plasma Na concentration showed only a small and non-significant decrease. The extracellular amount of Na thus increased, which Ledingham explained by the decrease of the intracellular amount of Na in the skeletal muscle. When the drinking water was replaced by 0.5% NaCl solution, the plasma Na concentration remained unchanged, the extra-

cellular volume increased more markedly, while the Na_i decreased slightly and the $[Na]_i$ remained unchanged in skeletal muscle. These findings concerning the electrolytes in the skeletal muscle do not agree entirely with those in present investigation, but they illustrate that differences in the water and electrolyte intake influence the results (compare the overhydrated series).

Rush & Randall (1957) found that the intracellular Na and Cl concentrations were increased, while the intracellular K concentration was unchanged in skeletal muscle 72 hrs after bilateral ureteric ligation in fasting dogs. The water, Na and Cl losses were, however, replaced intravenously. The intracellular volume of the skeletal muscle increased, while the extracellular volume decreased, as determined by inulin and sucrose.

Gessler & Calbie (1960) found that H_2O_m , Na_m , K_m and Cl_m of skeletal muscle in rats allowed free access to food and water were significantly increased 33 hrs after nephrectomy. These observations were corroborated by the present study.

Fishman & Raskin (1967) also found that the amounts of water, Na and K per 100 g solids in the quadriceps muscle in rats allowed free access to 5% glucose solution were increased 48 hrs after nephrectomy. In that study, however, the Cl content was unchanged.

Irwin & Dow (1966) found that H_2O_m , K_m , Cl_m and $H_2O_e^{Cl}$ were increased, while Na_m was unchanged in skeletal muscle 48 hrs after nephrectomy in rats. The rats were allowed food and water *ad lib* until 16 hrs before killing.

Hagemann et al. (1969) observed an increased H_2O_m , H_2O_i , K_m and K_i , while $[K]_i$ and Cl_m were unchanged and Na_m , Na_i and $[Na]_i$ decreased according to the Cl-space in skeletal muscle in rats after 2 days of anuria.

Klinkman et al. (1963–64) and Klinkman (1970) found an increased K_m , K_i , Na_m and H_2O_m , while Na_i and H_2O_i determined by means of the Cl-space were unchanged in skeletal muscle in dogs 2–3 days after bilateral ureteric ligation with free access to water and food.

In a clinical study on the electrolyte-fluid content in skeletal muscle in ten cases of oliguric acute renal failure Graham et al. (1971) obtained widely varying and non-conclusive results.

In human acute renal failure Bergström & Hultman (unpublished observations) found that H_2O_m , and $H_2O_e^{Cl}$ and Na_m were often increased in skeletal

muscle, while K_m and Cl_m were unchanged. That K_m and Cl_m were not increased in their study may be ascribed to the fact that the mean plasma K concentration was only moderately increased. In their study as well as in the present study K_i was found to

be correlated with the plasma K concentration.

The changes observed in electrolyte-fluid composition of the skeletal muscles after nephrectomy in the present study thus agreed relatively well with those described earlier.

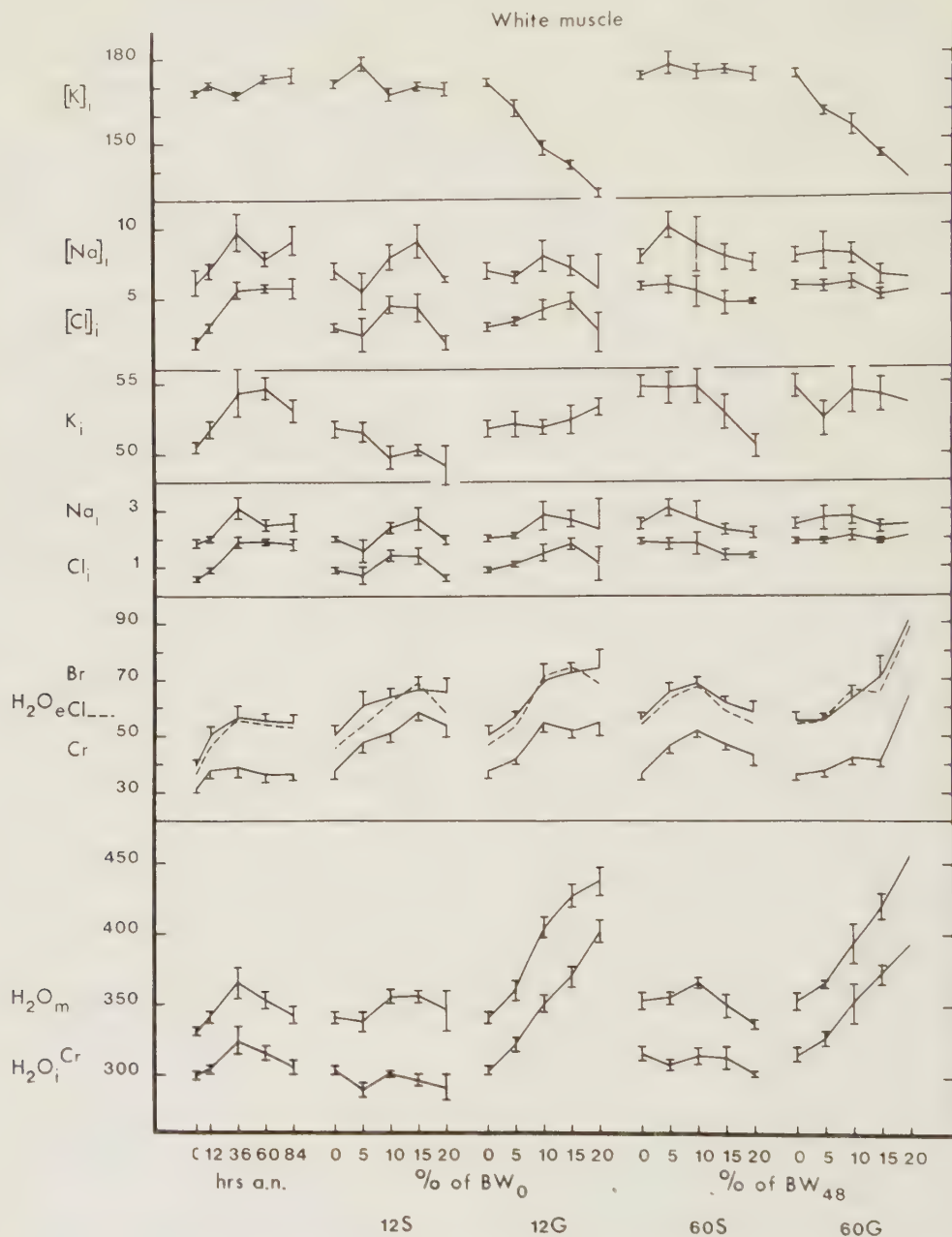


FIG. 15. Effect of nephrectomy and nephrectomy plus overhydration on the white skeletal muscle variables determined (ml or mEq/100 g FFS). For further explanation see fig. 1.

The changes observed in the intracellular amount of water, K and Cl are compatible with the assumption that if the K supply exceeds the capacity of the body to store and excrete K, the plasma K concentration will increase and K, together with Cl and water, is

passively distributed into the intracellular compartment (see Bergström 1964).

The observed decrease in the ratio $[Na]_e / [Na]_i$ in the white skeletal muscle suggests that also a reduction in the Na-K pump activity owing to the uraemia

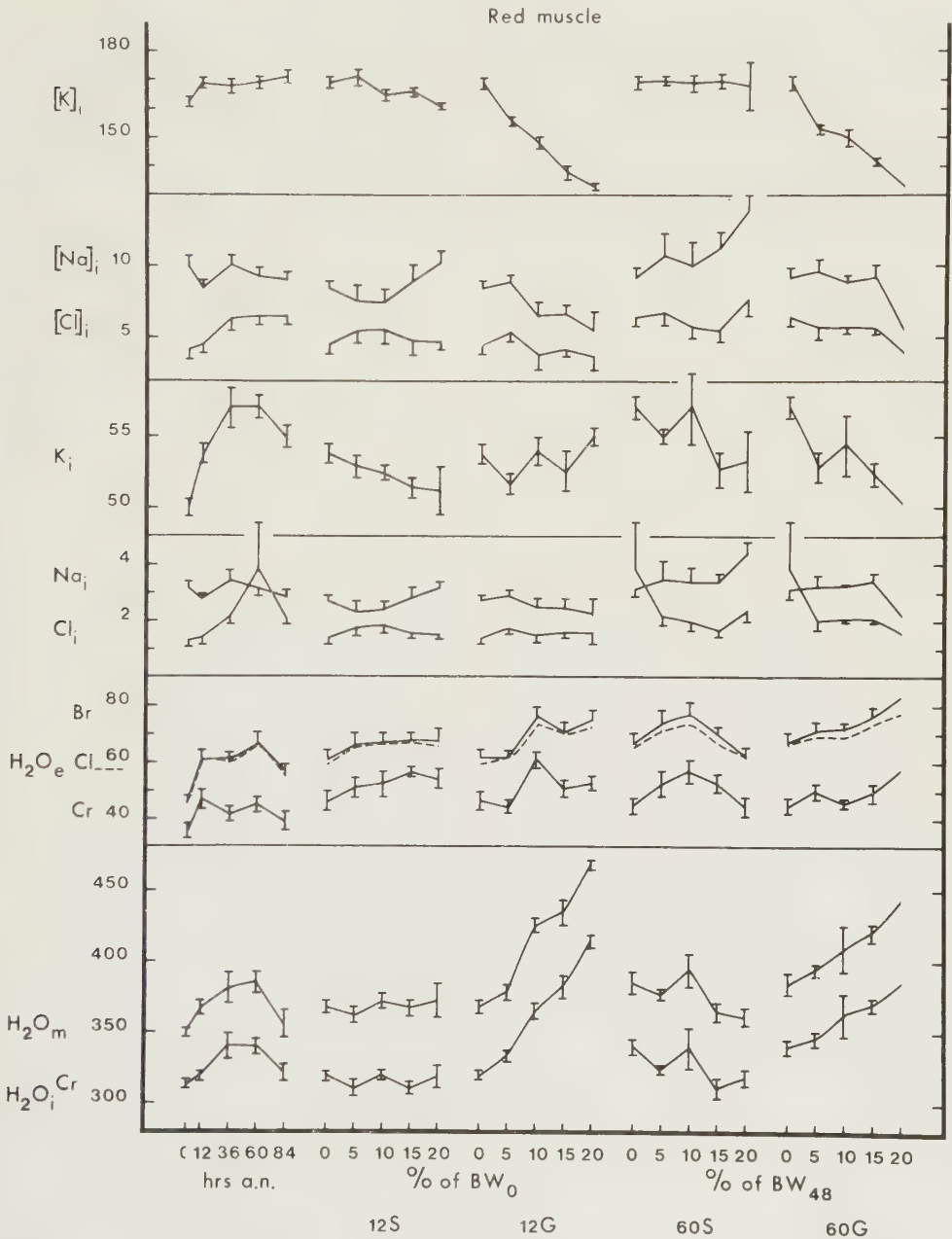


FIG. 16. Effect of nephrectomy and nephrectomy plus overhydration on the red skeletal muscle variables determined (ml or mEq/100 g FFS). For further explanation, see fig. 1.

might have contributed to the decrease of the ratio $[K]_i / [K]_e$, which is in agreement with the finding that the uraemic plasma contains a humoral inhibitor of the active Na-K transport (Bittar 1969, Bergström & Bittar 1969, Bricker et al. 1970, Bourgoignie et al. 1971).

A decrease in the glycogen content of the muscles because of the operative trauma and the acute renal failure should not have influenced K_i , as the amount of intracellular K per 100 g FFS is of the same magnitude as the amount of K "bound" to 100 g glycogen (45 mEq) (Bergström et al. 1967). Such a decrease may, however, contribute to an increase in Na_i and Cl_i .

The reduction of the membrane quotients for the electrolytes determined probably reflected a reduction of the membrane potential, which has been observed in uraemia (Bolte et al. 1963, Röhl 1964).

The intracellular pH in acute uraemia does not appear to be reduced (Irvine & Dow 1966, Stryjecka-Rowinska 1968), but the increasing extracellular acidosis must reasonably have contributed somewhat to the electrolyte-fluid changes observed in skeletal muscle.

12S and 60S. H_2O_m in WM increased nearly significantly in the 12S-series. Otherwise no significant changes were noted in H_2O_m or $H_2O_i^{Cr}$ in WM or RM in either of the saline overhydrated series. It is clear from Fig. 15 and 16, however that $H_2O_i^{Cr}$ decreased slightly numerically in WM and RM in the two series. The $H_2O_e^{Cr}$ in WM and RM increased relatively linearly in the 12S-series, but increased hyperbolically, with a maximum at 10% overhydration, in the 60S-series.

K_i of the WM and RM decreased in both series. $[K]_i$, however, did not change. Na_i did not change clearly. This also holds for $[Na]_i$ with the exception of RM in the 60S-series in which $[Na]_i$ increased almost significantly. $[Cl]_i$ of WM decreased significantly in the 60S-series. Otherwise no significant changes of Cl_i and $[Cl]_i$ were noted in the two muscles.

In the 12S-series no significant changes were found in the ratios $[K]_i / [K]_e$, $[Na]_e / [Na]_i$, $[Cl]_e / [Cl]_i$ and $[Br]_e / [Br]_i$. In the 60S-series, on the other hand, an increase was noted in the ratios $[K]_i / [K]_e$, and $[Br]_e / [Br]_i$ in both RM and WM and $[Cl]_e / [Cl]_i$ in WM.

The findings suggest that the saline overhydration resulted in mild dehydration of the skeletal muscles,

and an associated small but definite intracellular loss of potassium. Overhydration did not seem to have a negative effect on the Na-K pump, but rather a positive effect in the 60S-series, in which the membrane ratios for the ions determined increased.

12G and 60G. H_2O_m and $H_2O_i^{Cr}$ of RM and WM increased linearly and considerably in the two glucose overhydrated series. The increase was smaller in RM in the 60G-series than in WM in the same series and in WM and RM in the 12G-series. Otherwise no significant difference was found between WM and RM or between the 12G and 60G-series. $H_2O_e^{Cr}$ of RM and WM increased or tended to increase in both series.

K_i in RM, but not in WM, decreased significantly in the 60G-series. In the 12G-series no clear change was noted in this variable in the two muscles. $[K]_i$ of RM and WM fell markedly in both series. The magnitude of the relative decrease was the same throughout.

$[Na]_i$ of RM decreased in the 12G-series. Otherwise no significant change was found in Na_i and $[Na]_i$ in the two series.

Cl_i and $[Cl]_i$ of WM and RM remained unchanged in both series.

The ratio $[K]_i / [K]_e$ of RM and WM decreased significantly in the 12G-series. This was also true for the ratio $[Cl]_e / [Cl]_i$ of WM in this series. Otherwise no significant changes were found in the membrane quotients for the electrolytes determined.

It is reasonable to assume that the muscle glycogen content increased somewhat in the two glucose overhydrated series (Bergström et al. unpublished observations). Such an increase does probably not influence K_m and K_i (see above) but may result in an underestimation of Na_m , Na_i , Cl_m and Cl_i .

The glucose overhydration thus resulted, as expected, in a marked increase in the intracellular volume of the skeletal muscle and an accompanying corresponding reduction of the intracellular K concentration. Though it is not known why RM in the 60G-series lost some intracellular K and presumably thereby accumulated less water intracellularly than the WM in that series, it does underline the existence of certain differences between red and white skeletal muscle.

Muldowney (1963) gave intact dogs an injection of vasopressin and overhydrated them with 2.5% glucose solution. He found that the amount of water per 100 g FFS in skeletal muscle was well correlated with the

TBW. Furthermore, in a clinical material he also found that the Na + K concentration per liter muscle water was correlated with the plasma Na concentration. There was thus good agreement between his findings and those of the present study.

SM-PREPARATION (Fig. 17)

C-12 hrs and 12-84 hrs. The SM preparation was made up of several tissues, such as bone, skeletal muscle, connective tissue, glandular tissue, nervous tissue, testes and the urinary bladder. The main components were, however, bone and skeletal muscle. The preparation was analysed mainly for the sake of completeness. As the preparation contained considerable amounts of Ca, the Na content must have been somewhat overestimated. Forbes et al. (1959) found that flame photometry overestimated the Na content of bone by about 7 percent. This error must have been smaller in the present investigation. Further, it must have been relatively constant and could therefore hardly have had any appreciable influence on the changes observed in the Na content.

The weight and the water content of the SM-preparation increased initially after nephrectomy and afterwards persisted at a higher level than that in the control series. The FFS increased nearly significantly initially after nephrectomy and afterwards fell nearly significantly to the same values as in the controls. The ECW, as measured with the three reference substances, increased hyperbolically. The increase in the ECW^{Cr} was less than those in the ECW^{Cl} and ECW^{Br} . ICW^{Cr} decreased hypobolically. The amount of K, Na and Cl in the SM-preparation increased in the initial phase after nephrectomy. The amounts of Na and Cl were then unchanged, while the amount of K decreased.

The initial increase in the amount of water, Na, K and Cl was probably mainly due to the fact that the absorption of these substances after nephrectomy initially exceeded their elimination. The small reduction in the amount of FFS during the 12-84 hr period after nephrectomy suggests that there was no substantial catabolism and/or glycogen consumption during the period in question.

That the ECW^{Br} and ECW^{Cl} increased more than the ECW^{Cr} might be ascribed to the increase in the

relative intracellular Cl and ^{82}Br concentration in, among other tissues, the muscles. That the K content decreased during the 12-84 hr period after nephrectomy may be partly explained by the fact that the K content of the red cell volume of the preparation decreased and partly by tissue breakdown.

The progressive acidosis was not accompanied by any notable liberation of bound Na from the skeleton described by Burnell (1971).

12S and 60S. The amount of water, the extracellular volume and the Na and Cl content of the SM-preparation increased considerably in the two saline overhydrated series. In the 12S-series the extracellular amount of water increased, as measured with the three reference substances numerically more than the total amount of water in the preparation, which suggests that the intracellular amount of water decreased somewhat in this series (see Skeletal muscle). This was not the case in the 60S-series, where the extracellular amount of water increased to the same extent as the total water amount (compare Total body). A certain shift of K from the intra to the extracellular space probably occurred, especially in the 12S-series (see Skeletal muscle).

12G and 60G. The water content of the SM-preparation increased numerically more in the two glucose overhydrated series than in the saline overhydrated series. The increase in the 60G-series was numerically larger than that in the 12G-series. Judging from the increase in the ECW^{Cr} , in the 12G-series the increase in the amount of water in the extracellular space constituted about 60% of the total water increase of the preparation. The corresponding figure for the 60G-series was about 70%. This implies that the increase in ICW^{Cr} of the SM-preparation was nearly significantly smaller in the 60G than in the 12G-series. The Na content decreased significantly in the 60G-series, but was unchanged in the 12G-series. The K content changed in the opposite way, but this could be explained by a slight, nearly significant decrease in the amount of FFS with increasing overhydration in the 12G-series. The Cl content was unchanged in the two series.

As will be apparent, the effect of glucose overhydration on the electrolyte-fluid distribution in the SM-preparation was largely the same as in the total body (see below).

The possibility that the skeleton and/or other extracellular structures may serve as depots for *inter alia* Na, gains no force from the findings in the present study (see Discussion).

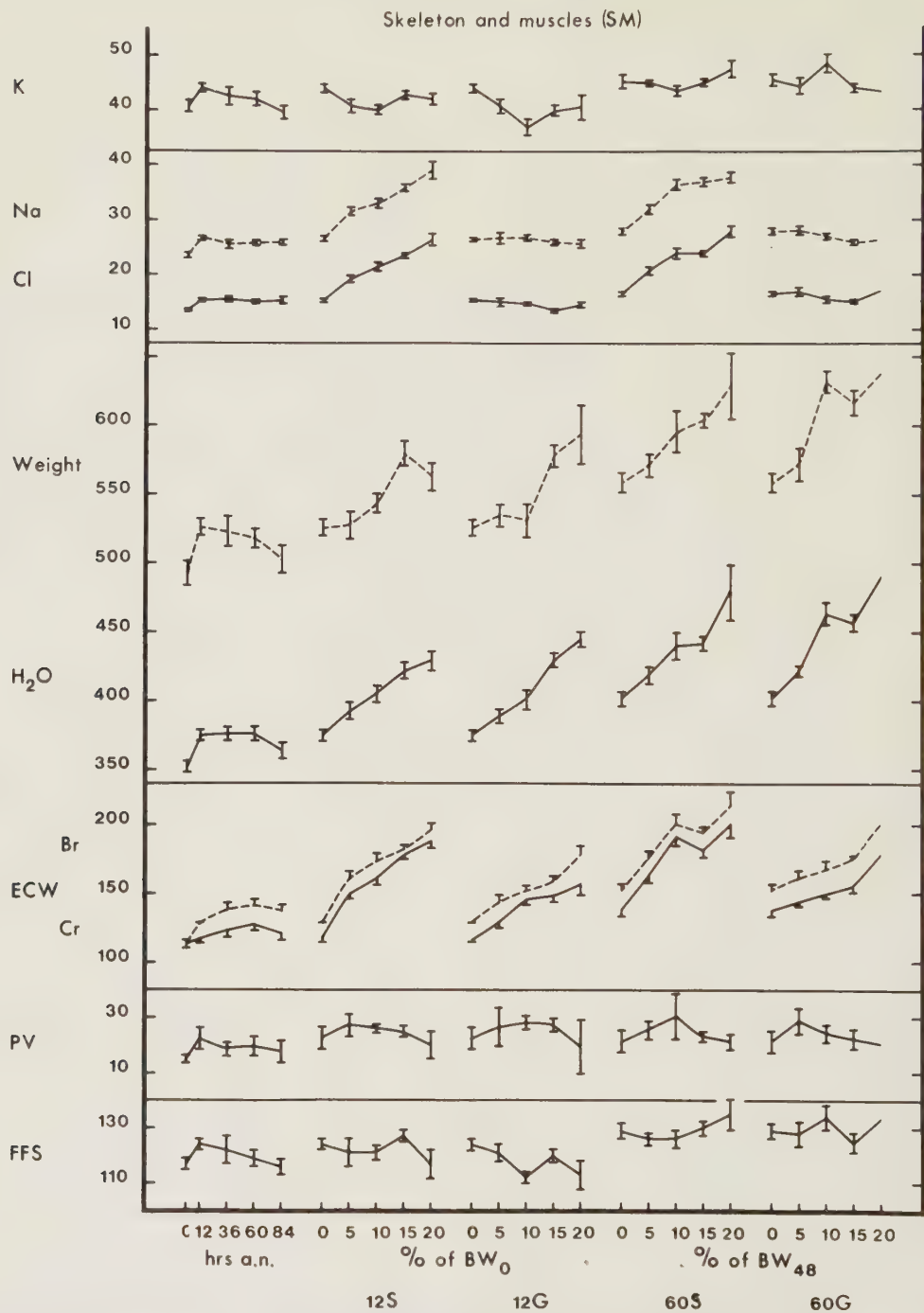


FIG. 17. Effect of nephrectomy and nephrectomy plus overhydration on the SM-preparation variables determined (g, ml or mEq/kg BW₀ and BW₄₈). For further explanation, see fig. 1.

TOTAL BODY (Fig. 18)

C-12 hrs. The values found for the total body variables determined in the control series were — after due consideration to the fact that the kidneys and the gastric contents were not included in the calculations — in close agreement with the values reported by others in the rabbit (Kruhoffer 1946, Aikawa 1950, Soberman 1950, Rodbard et al. 1951, Murihead et al. 1952, Nadel et al. 1956, Sweet et al. 1957, Gotch et al. 1957). A higher value for ECW_B^{Br} than for ECW_B^{Cl} as was observed here has also been found in dogs by Gamble & Robertson (1952). ECW_B^{Cr} was clearly smaller than ECW_B^{Cl} and ECW_B^{Br} in the 12 hr-series. ECW_B^{Cr} must, however, have been larger than the true ECW_B . The latter is not known, but it is reasonable to assume that it is about 15–20% of the kidneyless bodyweight. Kruhoffer (1946) found that the inulin-space was about 14–18% of the kidneyless bodyweight in rabbits weighing 2.5–3.0 kg, 2–12 hrs after nephrectomy (= the equilibration time). ECW_B determined by ^{131}I -C1-propylinulin in 11 rabbits treated in the same way as the animals in the 12 hr-series was found to be 261 ± 20 ml/kg BW_0 in a pilot study; a value that corresponded well to the ECW_B^{Cr} in the 12 hr-series in the present study.

No notable difference was found between BW_0 in the 12 hr-series and that in the controls. The bodyweight fell by about 17 g more in the control series than in the 12 hr-series during the 12 hrs the animals were deprived of food and water in spite of the fact that the animals in the control series had received 40–50 ml of 0.9% saline solution intravenously during this period. The difference may be ascribed largely to the fact that the animals in the 12 hr-series had a larger amount of gastric contents (mean diff. 11.6 g/kg BW_0 , $p < 0.02$) and TBW (10 ml $p > 0.05$).

The values found for ECW_B^{Br} , PV_B , RCV_B and TBK were significantly larger and ECW_B^{Cl} and TBNa numerically larger in the 12 hr-series than in the control series. No difference in magnitude was found in TBS or TBC1 between the two series.

The difference between the 12 hr and the control series regarding TBW, TBNa and TBK may reasonably be explained by the fact that the animals in the control series excreted the water, Na and K resorbed from the intestinal lumen during the 12 hrs via the urine. That the difference in TBW was not so very large

between the two series may be explained by the fact that the gastric contents, which were not included in the TBW-calculations, were larger in the 12 hr-series than in the control.

The reason why ECW_B tended to be larger in the 12 hr-series than in the control series may be, among other things, that TBW and TBNa were numerically larger and that the extracellular amounts of K, Ca and Mg were clearly larger in the 12 hr-series than in the controls. This was, however, partly counterbalanced by an increase in the intracellular amount of K in some tissues (e.g. red cell, skeletal and cardiac muscle).

That PV_B was notably larger in the 12 hr-series than in the controls might be explained by the assumed increase in ECW_B in the 12 hr-series, which may have caused the increase observed in the intravascular amount of proteins as a consequence of an increased lymph flow. The difference in RCV_B between the 12 hr-series and the controls must have been due to a liberation of red cells from their depots in the 12 hr-series.

12–84 hrs. There was no correlation between the time interval after nephrectomy and BW_0 . During the 12–84 hr period after nephrectomy BW_A fell according to linear regression analysis by about 33 g/kg BW_0 per 24 hrs. About 8 g (25%) of this reduction in weight may be ascribed to reduction of gastric contents. Of the remaining weight loss (about 25 g/kg BW_0) about three fourths was due to loss of water and about one fourth to loss of solids. The relative reduction of TBW and TBS was of the same order (2.8 and 3.0% per 24 hrs, respectively). No change was found in the TBF.

TBW remained unchanged during the 12–36 hr period after nephrectomy and afterwards decreased by about 22 ml/kg BW_0 per 24 hrs. This non-linear course could be explained by a reduction of the gastric contents by about 21 g/kg BW_0 during the 12–36 hr period followed by a reduction by only 5 g/kg BW_0 during the rest of the period studied. The rate of water loss from the total body seemed thus to be of the same magnitude throughout the 12–84 hr period after nephrectomy. The water balance was thus not influenced by changes in respiratory pattern, body temperature and uraemic enterocolitis.

ECW_B determined by the three markers used tended to increase, while TBW decreased, which means that ICW_B^{Cr} decreased. The reduction of ICW_B^{Cr} and the increase of ECW_B^{Cl} , ECW_B^{Br} and ECW_B^{Cr} were not

linear but hypobolic and hyperbolic, respectively, with a minimum and a maximum, respectively, at 60 hrs after nephrectomy. These events may be ascribed to, among other things, a non-linear change in the absorption of water and electrolytes from the gut. That ECW_B^{Cl} and ECW_B^{Br} increased was also due to an overestimation because of a relative increasing intracellular Cl and ^{82}Br concentration in some tissues.

In the 12 hr-series ECW_B^{Cr} was clearly less than ECW_B^{Cl} and ECW_B^{Br} . During the 12–60 hr period after nephrectomy, ECW_B^{Cr} increased more than ECW_B^{Cl} and ECW_B^{Br} with the result that ECW_B^{Cr} was equal to ECW_B^{Cl} in the 60 hr-series. ECW_B^{Cr} afterwards fell markedly during the 60–84 hr period while ECW_B^{Cl} and ECW_B^{Br} showed only a slight numerical reduction during this period. These events may be explained by the fact that DV^{Cr} increased hyperbolically in the intestinal preparation and decreased linearly in the liver, while DV^{Cl} and DV^{Br} remained unchanged in these organs.

That the observed hyperbolic increase of ECW_B^{Cl} , ECW_B^{Br} and ECW_B^{Cr} was not simply a consequence of increased respectively decreased penetration of the reference substances to the intracellular phases, but also to a true hyperbolic increase of ECW_B is supported by the observation that the amount of ascitic fluid and pericardial effusion also showed a hyperbolic course during the 12–84 hr period after nephrectomy. It was also striking that the plasma Na and Cl concentrations decreased and the plasma K and Mg concentrations increased hypobolically and hyperbolically, respectively.

$TBNa$ and TBK decreased significantly. TBK decreased relatively more than $TBNa$. The $Na + K$ loss was relatively larger than that of water. The $TBCl$ remained unchanged. The extracellular amount of Na and K measured with ^{51}Cr -EDTA as extracellular marker increased from 37.7 ± 1.1 respectively 1.4 ± 0.7 mEq/kg BW_0 12 hrs after nephrectomy to 42.1 ± 1.4 and 2.7 ± 0.10 mEq/kg BW_0 , respectively, 60 hrs after nephrectomy and afterwards fell to 37.1 ± 1.3 respectively 2.0 ± 0.13 mEq/kg BW_0 84 hrs after nephrectomy. Judging from these figures then, the reduction found in the plasma Na concentration was a consequence of dilution and not to a real loss of Na from the extracellular compartment. The calculated increase of the extracellular

amount of K was of the same magnitude as the reduction of the amount of K in the RCV_B during the corresponding period.

PV_B tended to decrease during the 12–36 hr period after nephrectomy and afterwards to persist at a somewhat higher level than that in the control series. The plasma protein concentration showed the opposite course, which means that the intravascular amount of proteins did not change significantly. These events can reasonably be explained by an increased capillary pressure (see the observed rise of BP and CVP). The calculated RCV_B presumably decreased mainly as a cause of increased haemolysis.

That $TBCl$ did not decrease may be explained by compensation of the faecal loss of Cl by reduction of the gastric contents.

Of the TBS reduction of 6.6 ± 1.7 g/kg BW_0 per 24 hrs about 2.6 g could be ascribed to a nearly significant reduction of the amount of fat free solids in the SM -preparation, reasonably as a consequence of catabolism. The rest of the loss of solids (about 4 g/kg BW_0 per 24 hrs) could be ascribed to the intestinal preparation and then represent the faecal loss of solids and the amount of solids resorbed and metabolised.

It has been found in clinical series that ECW_B increases and ICW_B decreases during the oliguric phase in acute renal failure (see Bluemle et al. 1956). Friedman et al. (1959) found that the inulin-space increased after nephrectomy in rats with free access to water and food. Ledingham (1954) made similar observations in rats maintained on electrolyte free food and water or 0.5% $NaCl$ solution. These findings were thus in agreement with the observed increase in ECW_B measured with Cl , ^{82}Br and ^{51}Cr -EDTA in the present investigation. Rush & Randall (1957) unlike the above mentioned authors found that inulin and sucrose-spaces decreased, while the calculated intracellular volume increased in dogs after bilateral ureteric ligation. In their investigation the water and electrolyte losses were replaced by intravenous infusion.

Muirhead et al. (1952) found that PV_B , RCV_B and BV_B were decreased 3 days after nephrectomy in rabbits with free access to food and water during the experiments. With the exception of the observed initial increase in the above mentioned variables the results

in the present investigation were in agreement with the findings by Muirhead et al. (l.c.).

12S and 60S. There was no correlation between the degree of overhydration and BW_0 in the two saline

overhydrated series. The increase found for BW_A , TBW, TBNa and TBCl did not differ significantly from the expected increase of 10 g, 10 ml respectively 1.54 mEq/kg BW_0 respectively BW_{48} per percent over-

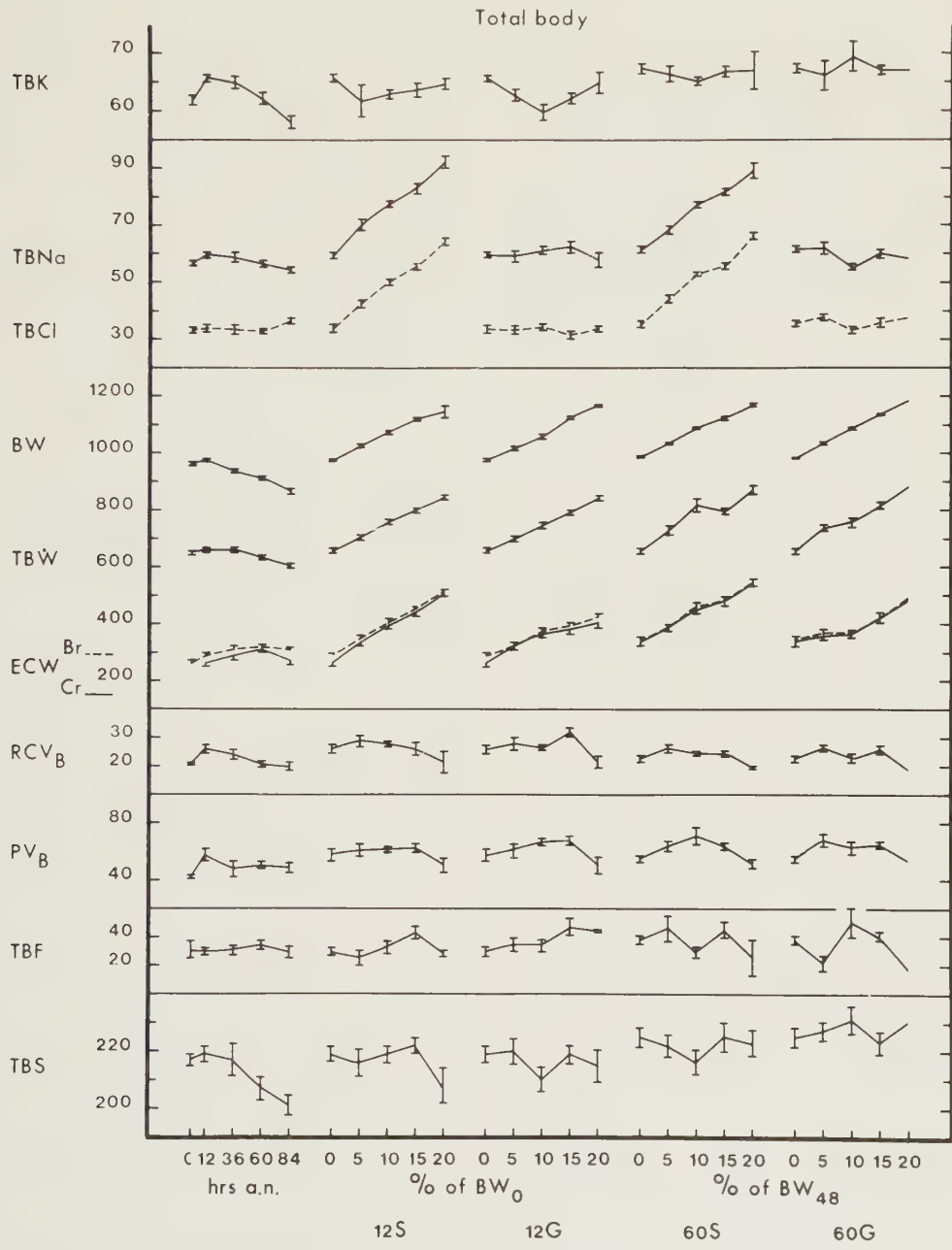


FIG. 18. Effect of nephrectomy and nephrectomy plus overhydration on the total body variables determined (g, ml or mEq/kg BW_0 and BW_{48}). For further explanation, see fig. 1.

hydration. No change occurred in TBS, TBF and TBK. Saline overhydration thus had no significant effect on the loss of water, solids and electrolytes from the body during the 12 hrs the animals were overhydrated.

In the 12S-series ECW_B^{Cl} tended to increase more and ECW_B^{Br} and ECW_B^{Cr} significantly more than TBW ($p < 0.01$ respectively $p < 0.005$), which means that ICW_B^{Cr} decreased in this series. In the 60S-series the ECW_B^{Cr} increased numerically more than TBW, while ECW_B^{Cl} and ECW_B^{Br} increased to the same extent as TBW.

The reason why ECW_B tended to increase more than TBW in the 12S-series may have been a somewhat lower effective osmolality of the extracellular fluid in the 12hr-series than that of the infused saline solution and an increase of extracellular amount of K, Ca, Mg and glucose. The extracellular amount of K calculated from ECW_B^{Cr} increased by 0.07 mEq/kg BW_0 per percent overhydration. That the difference between the increase of TBW and ECW_B tended to be smaller in the 60S-series than in the 12S-series may be partly explained by the extracellular amount of K and Mg not tending to increase in this series. The extracellular amount of Na calculated from ECW_B^{Cr} tended to increase more than TBNa in both series (1.75 against 1.56 mEq/kg BW_0 respectively 1.61 against 1.37 mEq/kg BW_{48} per percent overhydration). This and part of the discrepancy between the increase of ECW_B^{Cr} and TBW may be explained by increasing permeability to ^{51}Cr -EDTA into some of the phases of the intracellular compartment, or by the assumption that ^{51}Cr -EDTA equilibrated more completely with the extracellular space with increasing degree of overhydration. Epstein et al. (1955) also found that the extracellular volume tended to increase more than the infused amount of saline solution in nephrectomised animals. In their study inulin and ferrocyanide were used as extracellular markers.

PV_B did not change significantly but, as is apparent from the figure, PV_B tended to increase to reach a maximum at 10–15% overhydration. A similar correlation between PV and degree of overhydration was found for the SM-preparation, the intestinal preparation, the stomach and the skin. These events are tentatively explained in the following way: At moderate degrees of overhydration the lymph flow increased and caused a shift of proteins from the interstitial

to the intravascular compartment. At higher degrees of overhydration the increase in lymph flow could not compensate for the decrease in the interstitial protein concentration.

12G and 60G. As in the saline overhydrated series there was no correlation between the degree of overhydration and BW_0 in the two glucose overhydrated series. The observed increase in BW_A agreed well with the infused amount of fluid. In other words, overhydration did not significantly affect the weight reduction during the last 12 hrs before sacrifice of the animals. A numerical difference was, however, found in both series between the increase in the BW_A and that in TBW. This discrepancy could be explained by a positive correlation between the degree of overhydration and the sum of TBS and TBF, which might be due to the infusion of 0.3 g glucose/kg BW_0 and BW_{48} per percent overhydration.

The relative increase in ECW_B measured with the three reference substances was notably larger than that in ICW_B . ECW_B^{Cr} and ICW_B^{Cr} increased, for example, in the 12G-series by 2.8 and 0.5% of the 12 hr-series' ECW_B^{Cr} and ICW_B^{Cr} , respectively, per percent overhydration. Corresponding values found for the 60G-series were 1.8 and 0.8%, respectively, of the 60 hr-series' ECW_B^{Cr} and ICW_B^{Cr} . The discrepancy between the relative increase in ECW_B^{Cr} and ICW_B^{Cr} was, in other words, smaller in the 60G than in the 12G-series.

TBW increased by 1.4% and 1.3% per percent overhydration, respectively, of the TBW of the 12 hr and 60 hr-series. If the glucose overhydration is considered as a pure water overhydration at sacrifice the relative increase in the extra and intracellular volume should have been the same provided that all the body water is freely diffusable, that no net shift occurs in the amount of osmotic active substances between the extra and intracellular compartments, that no differences occur between the extra and the intracellular compartment regarding the change in the relation between the concentration of osmotic active substances and their effective osmotic activity and that the extra and intracellular spaces can increase without any change in hydrostatic pressure difference between them.

The infusion of glucose may have influenced the distribution of water between the extra and the intracellular compartments in many ways, but the

magnitude of such an influence must reasonably have been small compared with the large difference found between the observed and the expected increase in ECW_B and ICW_B . The explanation must instead be either that the increase in ECW_B was overestimated because the marker concentration in some phases did not fall parallel to the plasma marker concentration and/or that the true ECW_B increased relative more than the intracellular compartment because of a relative reduction of the intracellular osmotic load and/or because bound Na was liberated from *e.g.* the skeleton.

As in the two saline overhydrated series, PV_B tended to increase hyperbolically in the two glucose-overhydrated series. The explanation for these events is probably the same as for saline overhydration.

The calculated RCV_B did not change significantly in any of the two series. The increase and decrease of the RCV_B because of hydration and osmotic hemolysis were, of the same magnitude.

TBNa and TBCl were unchanged in both series. The plasma Na concentration decreased exactly as much as was expected if the extracellular amount of Na was unchanged and the relative increase in ECW_B was the same as that in TBW in both series. This fact suggests that no significant amounts of bound Na were liberated from *e.g.* the skeleton, but it does not exclude a shift of Na + water from the intracellular to the extracellular compartment. According to ECW_B^{Cr} the amount of Na in the extracellular fluid increased by 0.42 ± 0.10 mEq/kg BW_0 per percent overhydration ($p < 0.001$) in the 12G-series. Such a considerable shift can hardly have occurred from the intra to the extracellular compartment.

The plasma Cl concentration decreased more than expected from the assumption that the relative increase in ECW_B was the same as that in TBW. That this was the case may be explained by a net shift of Cl from the extra to the intracellular compartment and/or a true relatively larger increase in ECW_B than in TBW.

TBK decreased nearly significantly in the 12G-series but was unchanged in the 60G-series. The TBK decrease in the 12G-series can presumably be ascribed to an increase of the faecal loss of K in this series as a consequence of an increased intraluminal K content (see Intestinal preparation). The plasma K concentration was unchanged in the 12G-series, which must have meant that the extracellular amount of K increased in this series.

In the 60G-series the plasma K concentration fell as much as expected if one assumes that the extracellular amount of K was unchanged, while ECW_B increased relatively to the same extent as TBW.

That the plasma Na + K concentration fell to levels roughly expected from the TBW increase is in agreement with the findings of other authors (Gamble et al. 1923, Lavities et al. 1935, Wynn 1955, Edelman et al. 1958, Muldowney 1963). Stormont & Waterhouse (1961) produced hypo-osmotic overhydration in patients with use of pitressin. In patients who developed severe water intoxication they found a very low serum Na concentration (100–114 mEq/l) that could not be ascribed solely to changes in salt and water balance. They felt that the binding of cations to mucopolysaccharides, proteins or bone increased during severe water intoxication.

GENERAL DISCUSSION AND SURVEY OF THE RESULTS

EFFECT OF NEPHRECTOMY ON THE ELECTROLYTE-FLUID DISTRIBUTION AND ON SOME CIRCULATORY VARIABLES

In the management of patients with acute renal failure the aim must not only be to prevent such obviously serious electrolyte-fluid disturbances as hyperpotassaemia, cerebral and pulmonary oedema, but also to maintain conditions as good as possible for the various cell functions, i.e., a normal "milieu interieur"

This requires thorough knowledge of the electrolyte-fluid disturbances following the acute loss of kidney function. Despite numerous investigations in this field it is difficult to obtain a comprehensive conception of the changes in the electrolyte-fluid distribution in acute renal failure. It was therefore thought desirable to undertake an investigation of a wide variety of variables in an endeavour to obtain a more all-round view of the changes in the electrolyte-fluid distribution in the mammalian body at different intervals after nephrectomy.

Rabbits were used as the experimental animals, because they are easy to handle and because their organs are large enough to provide sufficient material for analysis. The normal electrolyte-fluid distribution in mammals differs somewhat with species, but, according to the literature, not notably in its reaction pattern to different manipulations. Only animals that appeared to be in a good general condition at the beginning of the experiments were used. During the experiments a few animals died in the longest series (the 84 hr series). Some of the surviving animals were, of course, sick, but none of them could be regarded as moribund.

Since many biological functions having a diurnal rhythm the manipulations and the sampling were performed according to a special time-table. The animals were always sacrificed in the morning. One of the reasons for this was that pilot studies had shown that during the investigation the bodyweight of the nephrectomised rabbits decreased more during the day than during the night.

To follow the events more than 84 hrs after nephrectomy was considered meaningless owing to the high rate of mortality and the very poor condition of the animals towards the end of the 84–108 hrs period after nephrectomy.

The possibility of obtaining true control values for the variables studied was somewhat limited by, among other things, the fact that the controls had to be given a continuous infusion of ^{51}Cr -EDTA during 12 hrs before sacrifice in order to obtain control values for the distribution of ^{51}Cr -EDTA in the animals. Since it was thought that this might possibly influence the normal intake of water and food, the conditions in this series were standardised in such a way that water and food were withdrawn at the beginning of the continuous infusion of ^{51}Cr -EDTA, which made it possible to distinguish the effect of nephrectomy from that of the deprivation of food and water on the variables of the gastro-intestinal tract. That this interference with the control animals did not affect the normal electrolyte-fluid distribution to any appreciable extent is corroborated by the observation that the results in this series agreed well with those obtained by others in normal rabbits. Since water and electrolyte intake after nephrectomy is of importance for the electrolyte-fluid distribution in the animals, this factor must be standardised. In contrast with many previous investigations, this was done in the present study by depriving the animals of food and water after nephrectomy. As the normal rabbit has voluminous gastro-intestinal contents, it was assumed that the deprivation of food and water would not have caused any symptoms of starvation and dehydration during the investigation period.

The reliability of the chemical and radioisotopic methods used were tested with duplicate determinations and found acceptable in a pilot study on twenty animals.

The electrolyte-fluid distribution is dependent not only on the input and output of water and electrolytes but also on the metabolism, hormones and the circulation. All this means that it is difficult to ascribe changes

in the electrolyte-fluid distribution after nephrectomy to any one particular factor. The kidneys not only excrete water, electrolytes and waste products, but also have at least two other essential homeostatic functions. They partake in the regulation of the circulation and the electrolyte metabolism via the renin system and in the regulation of erythropoiesis via the erythropoietin system. In addition, they are believed to have several hitherto poorly known functions, which may sometimes influence the electrolyte-fluid distribution. The kidneys, for example, contain significant amounts of vasodepressors and the loss of these may play a role in the development of renoprival hypertension. The kidneys also take part in the metabolism of the thyrotropic hormone, parathormone and insulin. Normally, the kidneys receive a relatively large part of the cardiac output, and the sudden loss of this part of the peripheral vascular tree must cause changes in the circulation which may have a secondary effect on the electrolyte-fluid distribution. The operative trauma and the experimental conditions in general must mean a stress for the animal, as does the clinical situation in cases of human acute renal failure, which inter alia via catecholamines and corticoids can influence the electrolyte-fluid distribution. The electrolyte-fluid disturbances per se act upon the cell metabolism and the release of hormones. Finally, the uraemic intoxication must affect the metabolism and thereby secondarily the electrolyte-fluid distribution.

The validity of all investigations of the electrolyte-fluid distribution is limited by the lack of a reliable marker for measurement of the extra and intracellular volumes. The reference substances hitherto used either penetrate into the cells and/or the gastrointestinal lumen and thus overestimate the extracellular volume or diffuse too slowly to some parts of the extracellular compartment, especially in the presence of extracellular oedema, and thus underestimate the extracellular volume.

The aim of the present study was, among other things, to evaluate ^{51}Cr -EDTA as a marker for the extracellular volume in the rabbit. From a physico-chemical point of view this substance should serve the purpose well, since it is a relatively small molecule (molecular weight = 359) and is well defined, and in a biological system it is stable and inert and has a very low lipid solubility and very little affinity with proteins (see Lökken 1969).

^{51}Cr -EDTA has been used as, among other things,

marker for the gastro-intestinal intraluminal compartment. In such studies less than 5% of the dose given by mouth is absorbed and appears in the urine (Lökken, 1969).

Given parenterally, less than 1% of the radioisotope is recovered in the faeces, the rest is eliminated completely with the urine within a few days (Lökken 1969). ^{51}Cr -activity persists longest in the liver and the spleen. The ^{51}Cr -EDTA complex does not penetrate into red cells (Lökken 1969, Garnett et al. 1967), and it is apparently unable to pass through the blood-brain barrier because of its low lipid solubility.

Another EDTA complex, $^{60}\text{Co(II)}$ -EDTA, has proved a good marker for the extracellular volume in smooth muscle (Brading & Jones, 1969).

On comparison between the ^{82}Br -space and the ^{51}Cr -EDTA-space in homo, Kunkel et al. (1968) found that the ^{51}Cr -EDTA-space was smaller than the ^{82}Br -space and that the size of the ^{51}Cr -EDTA-space agreed well with the values given in the literature for the inulin-space.

Virgilio et al. (1970) compared the distribution volumes of ^{14}C -carboxy-inulin and $\text{Cr-EDTA}^{14}\text{C}$ in nephrectomised baboons and found that both substances adequately reflected the extracellular-fluid volume in this species. The plasma disappearance curves for inulin and Cr-EDTA after an intravenous injection were followed for six hours. The curves for the two substances were found to be largely identical. After a rapid decrement phase during the first two hours, there followed a linear phase with a nearly significant negative slope. The latter slope was numerically somewhat steeper for inulin than for Cr-EDTA . The authors interpreted this numerical difference as a sign that Cr-EDTA equilibrated quicker and more completely with some phases of the extracellular space and penetrated less rapidly into the intracellular space than did inulin. That part of the continuous decrement may have been due to a successive increase of the extracellular space after nephrectomy was not discussed. Because of the continuous fall in the plasma inulin and the Cr-EDTA concentration, the distribution volumes of the substances were calculated from the plasma concentration at time zero extrapolated from the final slope. The distribution volume calculated in this was for Cr-EDTA numerically somewhat larger than for inulin (214 ± 3.7 against 185 ± 2.5 (SD) ml/kg BW). But it was not taken into account

that Cr-EDTA is a negatively charged substance with a Donnan factor of about 1.06 at physiological pH. When it was, the discrepancy given above between the distribution volumes of inulin and Cr-EDTA decreased about 10 ml/kg BW at a plasma volume of 50 ml/kg BW.

In the present study the author used not only ^{51}Cr -EDTA, but also ^{82}Br and the endogenous C1 as extracellular markers, two anions almost similar in their distribution pattern in the body. The reason why ^{82}Br was used besides the endogenous C1 was partly that it was not possible to decide how much of the skin chloride was extracorporeal and partly that objections had been raised against the method used in the present study for determining the amount of chloride in tissues (Cotlove 1963).

^{82}Br and C1 belong to those markers which overestimate the extracellular volume, because they penetrate into the gastro-intestinal lumen and into cells (particularly red cells, gastric mucosal cells and testicular cells) and, in addition, these ions seem to be bound to some extent to connective tissue structures (Cotlove 1954, Langgård 1965). By excluding the ^{82}Br -activity and the amount of C1 in the RCV_B and the gastric contents in the calculation of ECW_B, some of these sources of errors could be reduced in the present study. As an example, it might be mentioned that ECW_B was reduced in this way by about 15% in the control series.

In a pilot study the plasma activity curves were followed at one hour intervals after an intravenous injection of ^{82}Br and ^{51}Cr -EDTA in 10 nephrectomised rabbits overhydrated to 15% of bodyweight with 0.9% saline solution. During the period 6–12 hours after the injection no demonstrable change occurred in the plasma ^{82}Br and ^{51}Cr -activity. An equilibration period of 12 hrs was therefore considered sufficient even if the equilibration may have been somewhat slower in some series in the present investigation than in the animals in the pilot study.

Observations made in the present investigation appeared to warrant the conclusion that ^{51}Cr -EDTA was a reliable marker for the extracellular space in skeletal and cardiac muscle and perhaps also in stomach, but not in the other tissues examined. It penetrated to some extent into the gastro-intestinal lumen. It seemed to penetrate into and perhaps accumulate in some cellular phase, especially in the

liver and spleen and was excluded by the blood-brain barrier.

The distribution of C1 and ^{82}Br was, on the whole, in good agreement with that found by other authors, e.g. that the ^{82}Br -space was significantly smaller and larger than the C1-space in the brain and the stomach, respectively. It was, however, somewhat puzzling that the ^{82}Br -space seemed to be somewhat larger than that of C1 in all the other tissues studied.

Opinions still differ on the degree of binding of water and electrolytes in tissues. According to one theory, the membrane theory, most of the water, Na and K are not bound inside or outside the cells, and according to another, the sorptional theory, most of the water and electrolytes are bound within the cells. The interpretation of the results varies with the theory used. In the present study the results were interpreted according to the membrane theory, which is the more widely accepted one.

As will appear from the results accounted for in previous sections, differences were often found between the first 12 hrs after nephrectomy and the period later on concerning the rate or the direction of the changes in the variables studied. It was therefore considered suitable to discuss separately the events observed within the first 12 hrs after nephrectomy and those that occurred later. Several hypotheses may be offered to explain why the changes after nephrectomy were often biphasic. First, reaction to the stress of the operation and of the experimental conditions was presumably more severe initially after the operation than later. Second, the organism must reasonably have required some time to adapt itself to some of the effects of nephrectomy e.g. loss of the renal vascular bed, the renin system and the kidney metabolism of the parathormone. Third, the rate of absorption of water and electrolytes from the gastro-intestinal tract exceeded the intestinal secretions of water and electrolytes and other extrarenal losses of water during the initial period after nephrectomy.

Nephrectomy was followed within 12 hrs by the following changes. Bodyweight of the nephrectomised animals decreased somewhat less than that of the controls because of water retention and a smaller decrease in the amount of gastric contents in the former. TBK increased considerably and TBNa increased somewhat, but not significantly, whereas TBCl remained unchanged. The increase in TBK + TBNa was relatively larger than that of TBW. The

water excess seemed to be distributed between both the extra and intracellular compartments. The increase in the intracellular amount of K was compensated for by an increase in the extracellular amount of Na, K, Ca and Mg. The separate tissues studied showed only numerical or nearly significant changes in the intra and extracellular volumes. It should, however, be observed that the interstitial volume of the lungs even decreased. The plasma volume increased considerably, presumably owing to an increase in the intravascular amount of proteins elicited by an increase in the extracellular volume and thereby an increased lymph flow. The red cell volume increased, too, probably as a result of an effect of the acute stress on the stores of red cells.

The plasma Na concentration remained unchanged, while the plasma K, Ca and Mg concentrations increased. This implies that the extracellular cation concentration increased, which in the intracellular compartment — at least in the red cells, the cardiac muscle and the skeletal muscle — was largely balanced by an increased K concentration. The plasma Cl, inorganic phosphate and HCO_3 concentration tended to decrease. The gap between the increase in the cations and the decrease in the anions studied was probably filled up by an increase in the plasma citrate and sulphate concentrations. The increase in the plasma Ca concentration is ascribed by earlier workers to an increased plasma citrate concentration. This postulation may also hold for part of the considerable increase observed in the plasma Mg concentration.

Changes appear to have occurred in both the peripheral and the pulmonary circulation. The blood pres-

sure, the central venous pressure and the heart rate increased, while the roentgenologic heart size appeared to diminish. These changes can probably be ascribed partly to the increased blood volume and to the acute stress of the situation. Also other factors not studied, such as the loss of the renin system and the renal prostaglandins might have contributed. The observed electrolyte-fluid disturbances do not appear to have had any decisive effect on the observed increase in the blood pressure. The decrease observed in the interstitial volume of the lungs may perhaps be ascribed to circulatory changes in the pulmonary circulation.

Changes recorded during the 12–84 hr period after nephrectomy. An unexpected finding was the increase observed in the blood pressure as other authors have denied the occurrence of renoprival hypertension in the rabbit. Though the present investigation could not contribute with any explanation of the pathogenesis of this form of experimental hypertension, it did not lend support to the assumption that electrolyte-fluid disturbances contribute to the causation of elevation in the blood pressure, as no change in blood pressure was found in the overhydrated series. The central venous pressure persisted at a relatively high level after the initial rise in spite of the fact that the blood volume tended to decrease. The increased central venous pressure did not appear to be due to cardiac insufficiency, because both the roentgenologic size of the heart and the heart rate remained unchanged during the period studied. Nothing can be said with certainty about the capillary pressure, but much suggested that it was increased; the central

	<i>Weight</i>	<i>Water</i>	<i>Solids</i>	<i>Na</i>	<i>K</i>	<i>Cl</i>
Total body	–33	–18.6	–6.6	–1.7	–2.5	–
Skin	–	–3.8	–	–0.6	–0.3	–
SM-prep.	–	–	(–2.6)	–	–1.4	–
Gastric cont.	–8.2					
Stomach	+1.1	+1.1	–	+0.16	–	+0.10
Intestinal prep.	–16.8	–12.8	–4.0	–1.2	–0.6	–
Liver	–	–	–	–	–	–
Spleen	–0.05					
Lungs	(+0.30)	(+0.25)	(+0.05)	+0.04	–	+0.03
Heart	+0.11	+0.08	+0.02	–	+0.006	+0.001

Change of weight, water, solids and electrolyte contents per 24 hrs in the total body and in some of the tissues examined during the period 12–84 hrs after nephrectomy. Nearly significant changes are given within brackets.

venous pressure, the blood pressure and the plasma protein concentration were increased and probably also the cardiac output.

The observed considerable fall in the rectal temperature presumably reflected a reduction in the basal metabolic rate. This assumption is supported by the

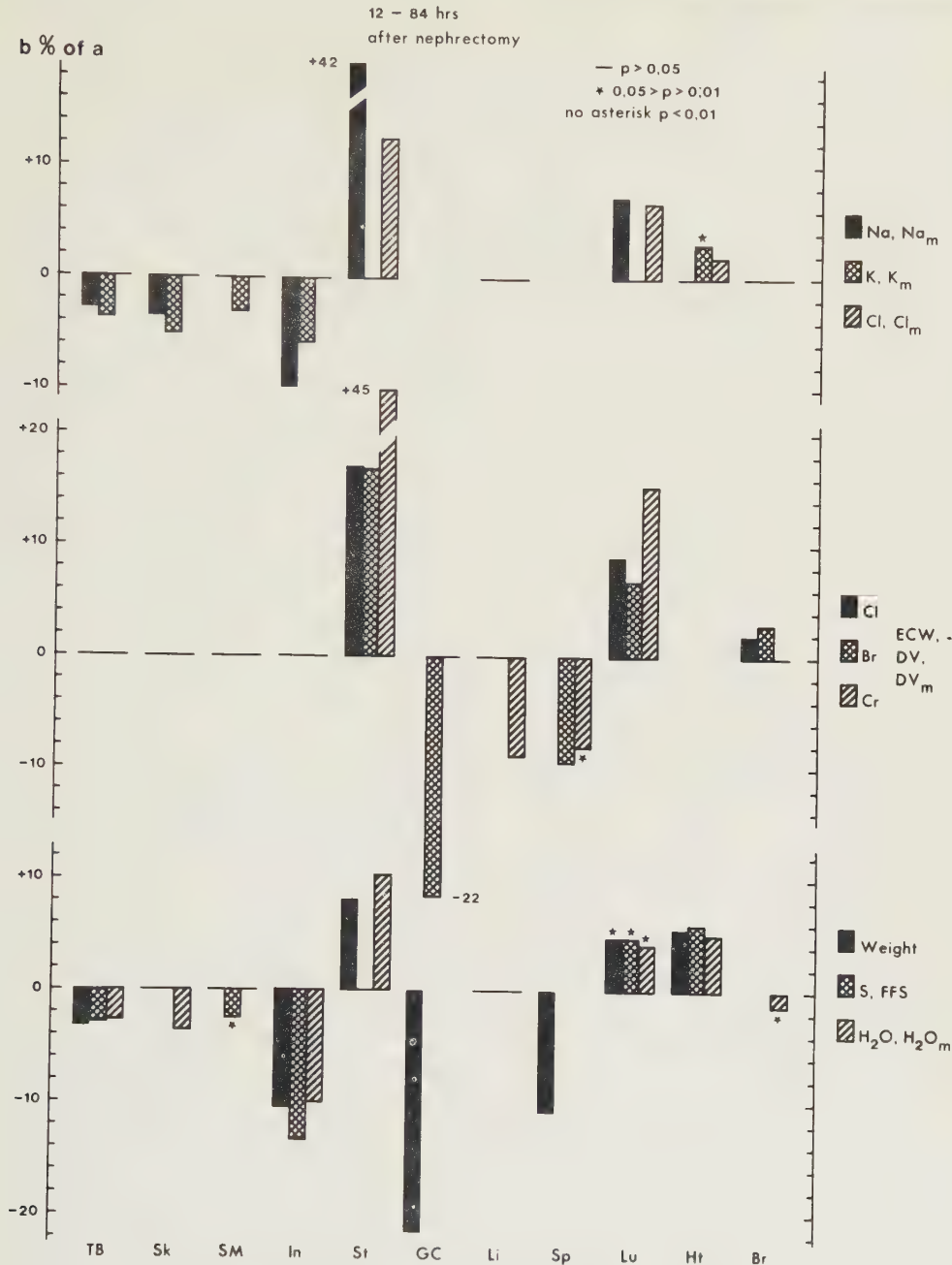


FIG. 19. Changes per 24 hrs, during the period 12 - 84 hrs after nephrectomy, of some variables of the total body and different tissues relative to the intercept, (the a -value) of the linear regression equation. Abbreviations for the different tissues: TB = total body, Sk = skin, SM = SM-preparation, In = intestinal preparation, St = stomach, GC = gastric contents, Li = liver, Sp = spleen, Lu = lungs, Ht = heart and Br = brain.

observation of Ledingham & Pelling (1970), who found a reduced oxygen consumption in rats three days after nephrectomy. Such a depression of the cell metabolism in general may, of course, have had an effect on the active ion transport.

The significant and almost significant changes in the weight, and in the water, solids and electrolyte content of the total body and the most important tissues are summarised in the table on page 68.

The values in the table denote the mean change per 24 hrs according to linear regression analysis. It should be pointed out that this type of statistical analysis does not always reflect the true course of events since some changes were not linear. Despite this objection the table gives a fairly good picture of the magnitude of the various changes. The relative changes in some of the variables studied expressed in percent of the intercept value of the linear regression equation per 24 hrs during the period 12–84 hrs after nephrectomy are summarised graphically in Fig. 19.

Bodyweight decreased during the 12–84 hr period after nephrectomy by about 33 g/kg BW_0 per 24 hrs. About one fourth of this reduction was due to a decrease in gastric contents, one fifth to the TBS and somewhat more than half to TBW. No significant reduction in TBF occurred, which suggests that the animals were not undernourished to any appreciable extent during the experiment. The relative decrease in TBW and that in TBS were roughly equal. Thus, the relative water content of the lean body remained unchanged.

TBW decreased by 2.8% per 24 hrs during the period studied. About two thirds of this water loss could be ascribed to the intestinal preparation, one fifth to the skin and the rest to the SM-preparation, in which the water content decreased numerically. An increase in the water content was observed in the heart and in the stomach. It increased almost significantly also in the lungs.

TBS decreased by 3.0% per 24 hrs during the period studied. About 60% of the total decrease could be ascribed to the loss of FFS in the intestinal preparation and the rest to a nearly significant reduction of the amount of FFS in the SM-preparation. The amount of solids in the heart and in the lungs increased significantly and nearly significantly, respectively.

TBNa and TBK decreased by 2.8 and 3.7%, respectively, per 24 hrs during the period studied. The decrease in TBK was thus relatively larger than that

of TBNa, which might have influenced the fluid distribution. The relative Na + K loss was larger than that of water, which must have influenced the electrolyte concentration within the body to some extent.

Two thirds of the TBNa decrease could be ascribed to the intestinal preparation and the rest mainly to the skin. The Na content increased in the stomach and in the lungs. The intracellular Na content and concentration increased in white skeletal muscle and red cells, it remained unchanged in red skeletal muscle and it decreased in cardiac muscle. No significant release of Na from the skeleton as a consequence of the increasing acidosis could be demonstrated.

Only one fourth of the decrease in TBK could be ascribed to the intestinal preparation, while about half and the remaining fourth could be ascribed to the SM-preparation and the skin, respectively. An increase in the K content could be recorded only in the heart. The intracellular K content increased in the skeletal muscle and decreased in the cardiac muscle and the red cells. The intracellular K concentration remained unchanged in skeletal muscle and decreased in cardiac muscle and red cells, numerically and significantly, respectively.

The total loss of K from the red cell volume was of the same magnitude as the increase in the extracellular amount of K.

TBCl was unchanged during the period studied. The Cl content increased in the heart, in the lungs and in the stomach. The intracellular Cl content and concentration increased in red cells, and in skeletal and cardiac muscle.

The changes in BW, TBS, TBW, TBNa and TBK were, as is apparent from above, largely due to the changes in the intestinal preparation, *i.e.* to changes in the amount of solids, water and electrolytes in the intestinal lumen. When the intestinal preparation was not included in the calculations, the following relative changes in the various variables were found: TBW – 1.1%, TBS – 1.4%, TBNa – 1.0% and TBK – 3.4%. It is clear from these figures that the discrepancy between the relative loss of Na and K and between the relative loss of Na + K and water was larger than when the intestinal preparation was included in the calculations.

ECW_B measured with Cl , ^{82}Br or ^{51}Cr -EDTA tended to increase hyperbolically, while the calculated ICW_B decreased hypobolically and somewhat more

than TBW. These findings may be explained in part by a successively increasing overestimation of ECW_B because of an increasing penetration of the markers into the intracellular compartment, and possibly to an increasing binding of the markers to extracellular structures. As far as ^{51}Cr -EDTA is concerned, such an overestimation was compensated for in part by a decreasing penetration of this substance into the intracellular compartment of the liver.

The DV of the three markers or the ECW calculated from them increased significantly or tended to increase in all the tissues studied with the exception of DV^{Cr} of the liver, which decreased significantly, DV^{Cl} and DV^{Br} of the intestinal preparation, which tended to decrease and DV^{Br} and DV^{Cr} of the spleen, which decreased significantly and nearly significantly, respectively. That the true ECW_B increased somewhat is suggested by the fact that the amount of ascitic fluid and pericardial effusion tended to increase along a hyperbolic curve similar to that for ECW_B and ECW of the SM-preparation.

According to linear regression analysis, ICW_B^{Cr} decreased by about 25 ml/kg BW_0 per 24 hrs during the period studied. This decrease was naturally overestimated for the same reasons as was the ECW_B . The decrease was also due to a decrease in the water content of the intestinal preparation. Most of this decrease (12.8 ml/kg BW_0 per 24 hrs) must, be ascribed to the intraluminal compartment. The reduction in the ICW_B^{Cr} , exclusive of the intraluminal water was thus notably less than that calculated. In the SM preparation ICW^{Cr} decreased by about 10 ml/kg BW_0 per 24 hrs. This reduction can presumably not be ascribed entirely to overestimation of ECW^{Cr} . It is, however, puzzling that the ICW^{Cr} of this preparation decreased, while the intracellular amount of water increased in the skeletal muscles, which presumably represented the bulk of the intracellular space of this preparation. The ICW decrease in the SM-preparation thus requires considerable dehydration of other cellular departments in this preparation.

In the stomach and in the intestines a breakdown of cells because of uraemic gastritis and enterocolitis, respectively, may have contributed to the decrease of ICW_B . The decrease in the red cell volume because of haemolysis naturally also contributed to a reduction of ICW_B . The amount of intracellular water in cardiac muscle was unchanged.

The distribution of water between the extra and intracellular compartment normally varies with the relation between the amount of Na + K outside and inside the cells. As pointed out above, the body lost a larger absolute and relative amount of K than of Na. The extracellular Na + K concentration increased somewhat during the period studied, which, provided that the extracellular space increased or remained unchanged, means that the osmotic load of these two cations tended to increase extracellularly. The change of the intracellular amount of Na + K in the individual tissues was not uniform, it increased in skeletal muscle and decreased in cardiac muscle and red cells. The total intracellular amount of Na + K in the body must have decreased, because, among other things, of breakdown of cells and decreased intracellular K-binding capacity owing to acidosis, protein catabolism, glycogen consumption etc. This must be the main cause of the assumed true ICW_B decrease.

The non-linear change in the extra and intracellular volume, of the plasma K and Mg concentration and of the intracellular amount of K in skeletal muscle must be ascribed mainly to a non-linear relation between the absorption and elimination of water and electrolytes.

There was evidence suggesting a reduced activity of the Na-K pump in the skeletal muscles and in red cells. A general depression of the active Na-K transport in the body should have contributed to an increase in the intracellular volume. Even if no such increase was observed, such a mechanism may have hampered the reduction of ICW_B and possibly contributed to the final tendency of ICW_B to increase.

EFFECT OF NEPHRECTOMY AND OVERHYDRATION ON THE ELECTROLYTE-FLUID DISTRIBUTION AND ON SOME CIRCULATORY VARIABLES

As mentioned, one of the commonest immediate cause of death in cases of acute renal failure was earlier overhydration with consequent pulmonary or cerebral oedema. In experimental studies on overhydration interest has therefore mainly been focused on the electrolyte-fluid distribution in the lungs and brain. Though the effects of overhydration on other organs do not produce any dramatic symptoms, they may nevertheless influence the clinical course. It would

also be of theoretical interest to know how the water and electrolyte excess in acute renal failure is distributed in the body and how the overhydration influences the electrolyte-fluid distribution in the individual organs. The answer to these questions could not be found in the literature. It was therefore thought to be of interest to try to find answers to these questions in association with the study on the effect of nephrectomy on the electrolyte-fluid distribution.

As the overhydration in the clinical situation is a consequence of an overload of water + Na or water alone (administration of electrolyte-free solutions) some animals were overhydrated with 0.9% NaCl solution and others with 3% glucose solution. Lower glucose concentrations were not considered suitable because of the risk of serious haemolysis during the infusion. The administration of glucose per se naturally affected the electrolyte-fluid distribution and then particularly during the glucose infusion and a certain time after the infusion because of hyperglycaemia. At sacrifice of the animals 10–11.5 hours after the glucose infusion the extracellular amount of glucose in the glucose overhydrated animals was somewhat increased, but the osmotic effect of this extracellular excess of glucose must have been small. It is difficult to assess the effect of the glucose administration on the intracellular osmotic activity at the time of sacrifice of these animals. An increase of the glycogen content and thereby of the intracellular K-binding capacity in certain tissues must presumably have occurred which makes it somewhat difficult to judge the variable referred to as fat-free solids. That the water was administered together with glucose might be of certain interest even from the point of view that the hypo-osmotic overhydration in the clinical situation is usually a consequence of excessive administration of carbohydrate solutions.

In order to find out whether any linear or non-linear correlation existed between the degree of overhydration and the variables studied, the animals were overhydrated to 5, 10, 15 and 20% of their bodyweight. Higher degree of overhydration was not considered of interest. To find out whether there was any difference in the effect of overhydration in the initial phase after nephrectomy and later on, some animals were overhydrated immediately after nephrectomy and others 48 hours later.

Saline overhydration. The saline overhydration had no demonstrable effect on the behaviour of the animals

in the 12S-series, while in the 60S-series it had, if anything, a favourable effect, possibly because of a dilution of uraemic factors or extracellular K and Mg.

The central venous pressure and the roentgenologic heart size increased, while the heart rate and the blood pressure persisted unchanged. The increase of the central venous pressure and of the roentgenologic heart size could not be explained by an increasing blood volume, but must have been due to other factors, such as an increased venous return, increased venous tone, changed intrathoracic pressure, and decreased myocardial contractility.

As expected, the water, Na- and Cl-excess seemed to be distributed to the extracellular compartment. In both series overhydration had also apparently resulted in a certain intracellular dehydration. This may perhaps be explained by, among other things, a higher effective osmolality of the infused solution than that of the extracellular fluid. In addition, the extracellular amount of K, Mg and glucose must have increased somewhat in the 12S-series and that of Ca and glucose in the 60S-series. That the endogenous increase of the extracellular osmotic load of K, Mg, Ca and glucose increased less in the 60S than in the 12S-series, may partly explain why ECW_B increased somewhat less in the 60S than in the 12S-series. Further, part of the discrepancy between the increase in TBW and that in ECW_B was surely due to some extent to a certain increasing overestimation of ECW_B .

The calculated ICW_B^{Cr} decreased significantly in the 12S-series and numerically in the 60S-series. These decreases could be ascribed largely to the skin, the SM-preparation and the intestinal preparation. The skeletal muscles showed only a numerical reduction of the intracellular amount of water. It was puzzling that the intracellular volume of the cardiac muscle seemed to increase in both series.

As expected, the water excess was found mainly in the skin, the SM-preparation and in the peritoneal cavity. Smaller, but significant, amounts were found in the pleural cavities and in the stomach (see Fig. 22). In the 12S-series a significantly larger amount of water was distributed to the peritoneal cavity than in the 60S-series, while the reverse was true for the stomach. Corresponding differences between the 12S and 60S-series were noted for the DV^{Cr} of the stomach (see Fig. 23).

The relative increase in the amount of water,

ECW^{Cr} , DV^{Cr} , DV_m^{Cr} and $H_2O_e^{Cr}$, respectively in the total body and in the tissues examined are summarised in Fig. 20, which shows that the extracellular volume did not increase to the same extent in all the tissues. This also holds for the increase in the interstitial amount of water in the tissues. This was not unexpected, since the factors, which regulate the interstitial volume must vary from tissue to tissue; the capillary and interstitial fluid pressure, the plasma and interstitial

colloid osmotic pressure, which in turn are dependent on the circulatory dynamics, the capillary permeability, the lymph flow and the interstitial space compliance (Guyton 1965). As expected, it was the skin that had the greatest relative and absolute capacity to cope with the excess of extracellular fluid except that of the stomach in the animals of the 60S-series, which showed the greatest relative increase of the water content and DV^{Cr} .

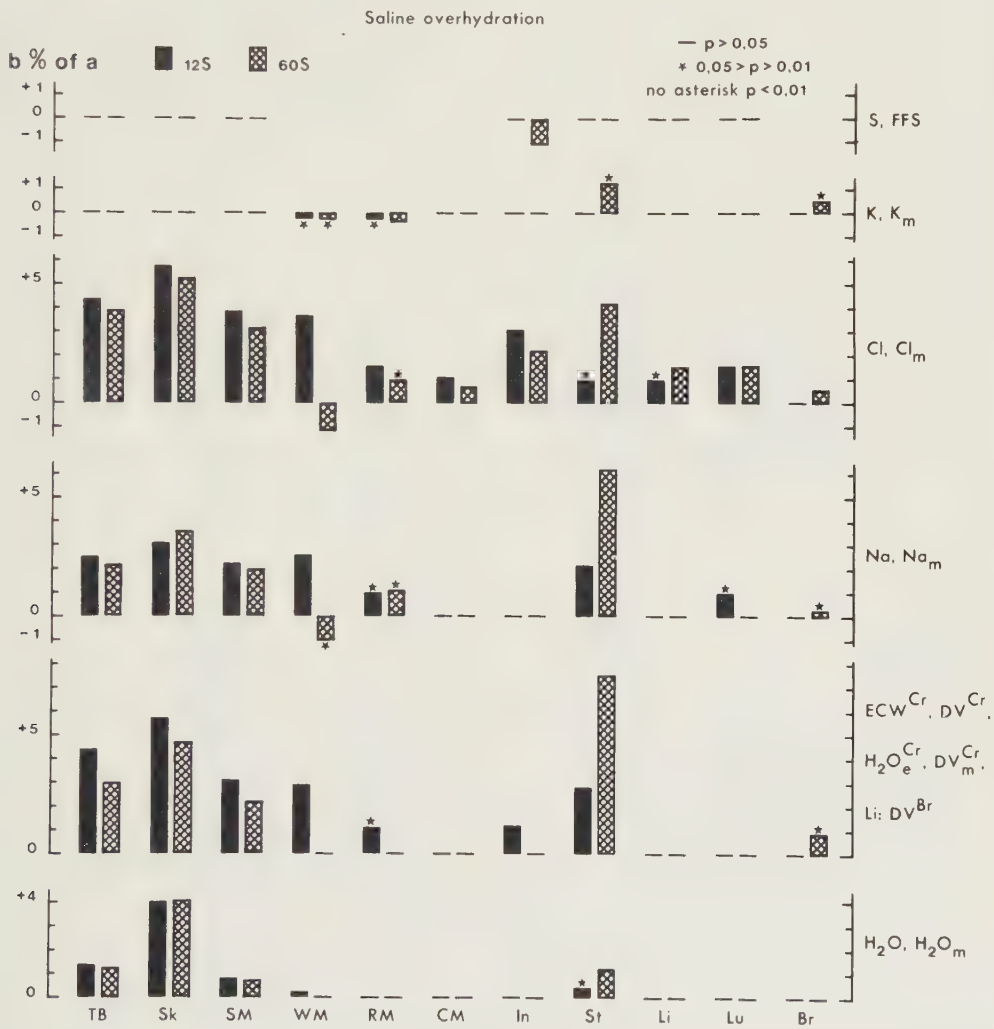


FIG. 20. The relative change of some variables in the 12S and 60S-series. The columns denote the change in per cent of the intercept (the a-value) of the linear regression equation, per percent overhydration.
 Abbreviations: WM and RM = white and red skeletal muscle, CM = cardiac muscle. For other symbols, see fig. 19.

The increases in the water content and in the variables used as measures of the extracellular water were linear except in the lungs, where these parameters increased hyperbolically in both series, in the stomach where they increased hypobolically in the 60S-series, and in the intestinal preparation, in the 12S-series where the water, but not the variables used for estimating the extracellular volume, increased to a high maximum at 10% overhydration and afterwards fell successively to control-level. No satisfactory explanation can at present be offered for these non-linear changes.

The distribution of the Na and Cl excess to the main tissues in the body is summarised in Fig. 24. For natural reasons the Cl excess was more evenly distributed among the different tissues, as the extracellular Cl concentration increased considerably in

both series. The Na excess was likewise naturally distributed according to the same pattern as the excess of the extracellular fluid. That relatively more of the Na excess than that of extracellular fluid was distributed to the SM-preparation, particularly in the 60S-series, may be explained by the fact that the extracellular Na concentration increased significantly in the 60S and tended to increase in the 12S-series.

The Na content of the intestinal preparation in the 12S-series, and in the lungs in both the series, and in the stomach in the 60S-series increased in the same non-linear manner as did the water content described above and the extracellular volume of the respective tissues. This was also true for the Cl-content, with the exception of the intestinal preparation, which must have been due to the increasing extracellular Cl concentration.

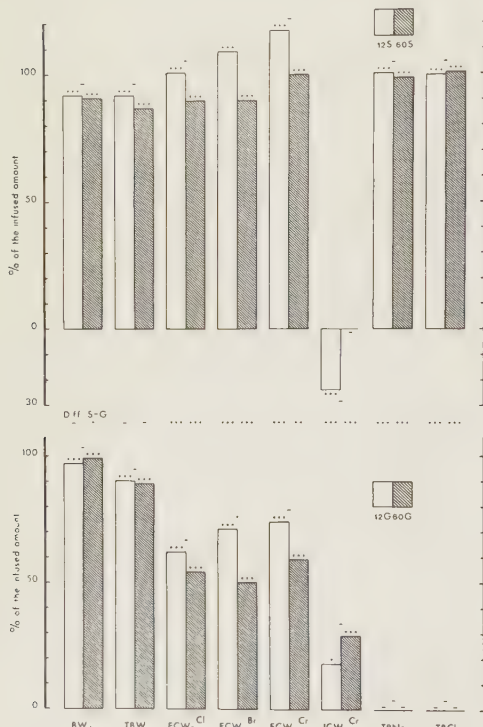


FIG. 21. Changes of some of the total body variables in per cent of the infused amount of water, Na and Cl, respectively. Significance of the increases and the difference between 12S and 60S and between 12G and 60G are given by asterisks above the columns. The difference between 12S and 12G series and between 60S and 60G are given under the heading diff. S-G. (- = $p > 0.05$, * = $0.05 > p > 0.01$, ** = $0.01 > p > 0.001$, *** = $p < 0.001$)

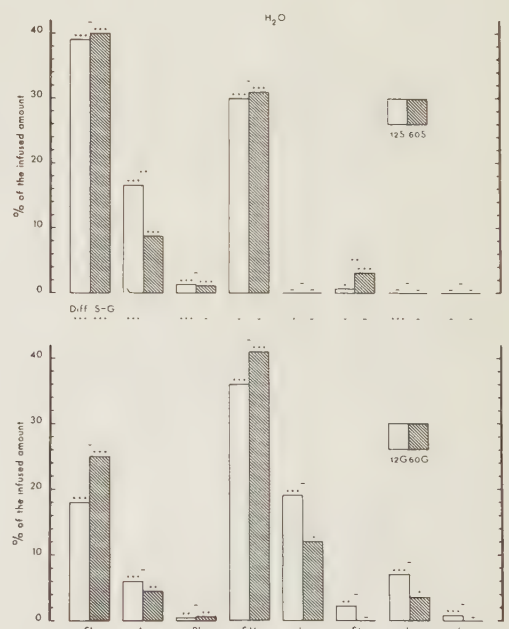


FIG. 22. Distribution of the water excess (the amount of water infused) in the overhydrated series calculated by linear regression analysis. Abbreviations: As = ascitic fluid, Pl = pleural effusion. For further explanation, see figs. 19 and 21.

Apart from the nearly significant increase in the intracellular Na concentration of the red skeletal muscle in the 60S-series, the intracellular Na-content and concentration of the skeletal and cardiac muscle did not change significantly. The red cell Na concentration increased considerably in the 12S-series, but was unchanged in the 60S-series.

The intracellular Cl concentration in the white skeletal muscle decreased significantly in the 60S-series, and the intracellular Cl content and concentration of the cardiac muscle increased nearly significantly in the 12S-series. Otherwise no notable changes were found in the intracellular Cl content or concentration in the skeletal and cardiac muscle. In both the series the red cell Cl concentration increased significantly.

With the exception of a decrease in the intracellular K content in skeletal muscle in the two series, the

intracellular K content and concentration of skeletal muscle, cardiac muscle and of red cells did not change significantly.

These findings, with the exception of the unexpected increase of the red cell Na concentration in the 12S-series, suggest that the active Na—K transport was not depressed by saline overhydration. In the 60S-series the active Na—K transport even seemed to have increased. This may have been due to dilution by the saline overhydration or correction of factors inhibiting the active Na-K transport.

Glucose overhydration. Heavy overhydration with glucose solution influenced the mental and motor activity of the animals, which could be ascribed mainly to the cerebral oedema observed. The muscular hypotonia observed may have caused a reduced lymph

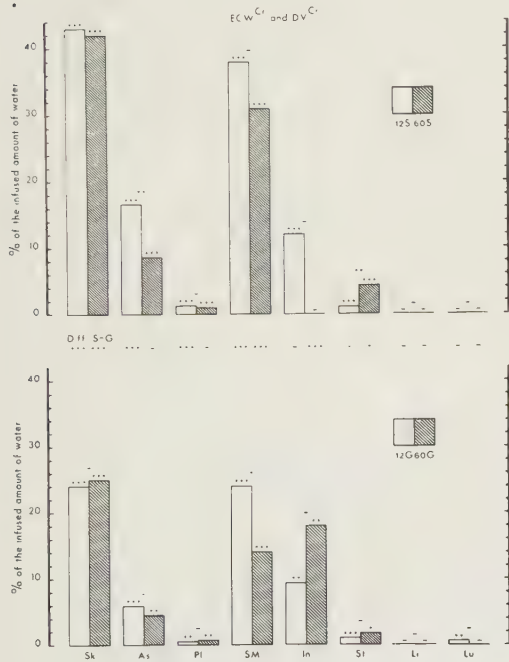


FIG. 23. Increase in ECW^{Cr} and DV^{Cr} in different tissues relative to the volume of water infused in the overhydrated series, calculated by linear regression analysis. For explanation of symbols, see figs. 19, 21 and 22.

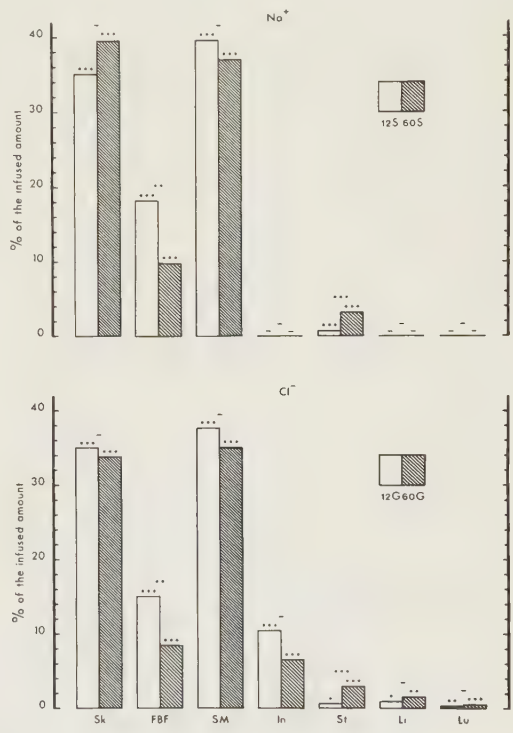


FIG. 24. Distribution of the Na and Cl excess, respectively, (the infused amount of Na and Cl) in the body in the 12S and the 60S series, calculated by linear regression analysis. For explanation of symbols, see figs. 19, 21 and 22.

flow and thus influenced the distribution of the extra-cellular fluid between the interstitial and intravascular compartment.

The circulation was affected in largely the same way as by saline overhydration, *i.e.* the central venous pressure and the roentgenologic heart size increased, while the blood pressure, the heart rate and the blood volume persisted largely unchanged. As in the saline overhydrated series, no satisfactory explanation could be found for the increase in the central venous pressure and the heart size in the glucose overhydrated series, but in view of the marked effective hypo-osmolality, the above mentioned changes were more likely due to decreasing myocardial contractility, as it has been shown that the tension developed by the cat papillary muscle is substantially reduced at hypo-osmolality (Koch-Weser 1963).

The rectal temperature fell significantly in the 12G-series, but was unchanged in the 60G-series, where the temperature was low from the very beginning. That the rectal temperature fell in the 12G-series might have ment that the basal metabolic rate decreased which might have influenced the active ion transport.

The water excess was more evenly distributed within the body in the glucose than in the saline overhydrated series (see Figs. 20, 22 and 25). The water content of the individual tissues increased largely linearly with the exception of that of the intestinal preparation in the 12G-series, where the water content increased hyperbolically and the lungs and the stomach in the 60G-series, where the water content increased hyperbolically and hypobolically, respectively. Moreover, the amount of water in the peritoneal cavity increased hyperbolically in the 12G-series. The relative increase in the water content did not appear to be uniform (Fig. 25). Among those tissues where the water increase seemed to be linear the relative increase was least in the cardiac muscle and in the brain in both the series, as well as in the red skeletal muscle in the 60G-series. In the cardiac muscle and in the red skeletal muscle this could be ascribed to a decrease in the intracellular Na + K content. The brain tissue lost Na + K, too, and it is reasonable to assume that part of these losses affected the intracellular compartment of the brain. The intracranial pressure must have had a decisive effect on the changes found in the electrolyte-fluid composition of the cerebral tissue.

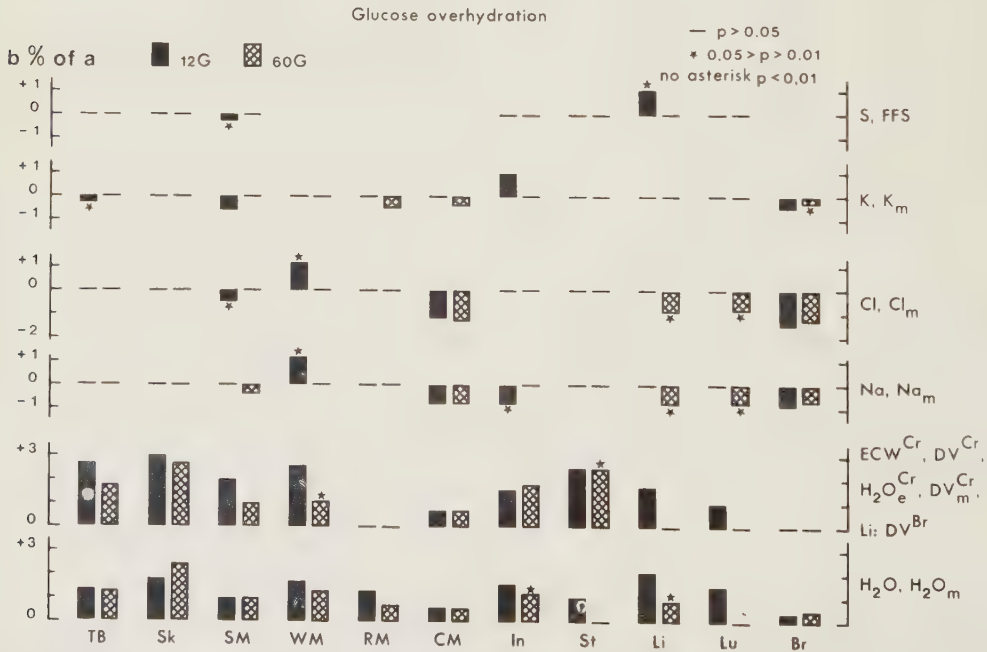


FIG. 25. The relative change of some variables in the 12G and 60G series. The columns denote the change in percent of the intercept (the *a*-value) of the linear regression equation per percent overhydration. For symbols, see figs. 19 and 20.

The relative increase in ECW_B , measured by $C1$, ^{82}Br and ^{51}Cr -EDTA, was considerably larger than that in the calculated ICW_B , especially in the 12G-series. Other observations, however, do not favour the assumption that the true ECW_B increased relatively more than ICW_B . It is true that the extracellular amount of K, Mg and glucose increased somewhat in the 12G-series and that of Ca and glucose in the 60G-series, but these relatively small increases in the extracellular osmotic load can hardly be sufficient to explain the observed large differences between the relative increase in ECW_B and ICW_B . Further, the decrease observed in the plasma Na + K concentration and in the intracellular Na + K concentration in skeletal muscle was not smaller than the reduction expected from the increase in TBW. This argues against liberation of Na from the skeleton to any appreciable extent, which might have otherwise explained the observed relatively large increase in ECW_B . This line of thought is supported by the fact that Forbes et al. (1965) could not demonstrate any significant decrease in the crystal Na in the bone in rabbits with hyponatremia. Neither did there appear to be any appreciable net shift of the electrolytes from the intraluminal compartment of the intestines to the extracellular compartment. The observed discrepancy between the relative increase in ECW_B and ICW_B as determined by means of the three extracellular markers used seemed therefore to be mainly the result of an overestimation of the increase in ECW_B . This assumed overestimation could not be referred to any particular tissue, as is apparent from Fig. 23.

ECW , DV or H_2O_e measured with the three reference substances appear to increase almost linearly in all tissues, except DV^{Cr} of the intestinal preparation, which increased hyperbolically and hypobolically, respectively, in the 12G and 60G-series. In the cardiac muscle $H_2O_e^{Cr}$ increased significantly more in the glucose than in the saline overhydrated series.

As in the saline overhydrated series, PV_B and PV increased hyperbolically in most of the tissues to a maximum at 10–15% overhydration. The reason why PV_B changed in this non-linear way in the glucose overhydrated series was probably the same as in the saline overhydrated series, i.e. that an increase in the intravascular amount of proteins at lower degrees of overhydration was at higher degrees of overhydration followed by a reduction of this factor, which among

other factors decides the plasma volume. As mentioned above, the decreased muscular activity might have contributed to the changes observed.

The glucose overhydration resulted in relatively marked osmotic hemolysis in both series. The calculated red cell volume was, however, unchanged, because of the hydration of the remaining cells.

Apart from a slight, nearly significant decrease in TBK in the 12G-series, glucose overhydration produced no changes in TBNa, TBK or TBC1. The slight decrease in TBK in the 12G-series may, perhaps, be related to the significant increase in the K content in the intestinal preparation, assuming the latter increase to have affected the intraluminal compartment with an accompanying increase of the K content of the faeces.

The intracellular Na content decreased nearly significantly in cardiac muscle in both series. The intracellular K content decreased significantly in red skeletal muscle in the 60G-series. The intracellular C1 content decreased significantly in cardiac muscle in the 60G-series. Otherwise no definite changes were found in the intracellular Na, K and C1 content in skeletal and cardiac muscle.

As the free body fluids increased relatively more than the extracellular volume in the tissues, electrolytes must have been withdrawn from the tissues. The magnitude of this withdrawal was, however, relatively small, with the result that it was difficult to specify the quantity of electrolytes withdrawn from the individual tissues. The only significant increase in the electrolyte content of the tissues was an increase in the K content of the intestinal preparation in the 12G-series, which was accompanied by a nearly significant reduction of the Na content, which was of the same magnitude as the K increase.

The plasma Na and C1 concentration decreased considerably in both series, as did the intracellular K concentration in skeletal muscle, cardiac muscle and red cells. The plasma K concentration was unchanged in the 12G-series, but fell significantly in the 60G-series. This means that the $[K]_i / [K]_e$ ratio decreased significantly in skeletal muscle, cardiac muscle and red cells in the 12G-series, but only numerically in the 60G-series. The intracellular Na concentration decreased significantly in cardiac muscle in both series as well as in red cells in the 60G-series, but not in red cells in the 12G-series or in skeletal muscle in any of the series. The $[Na]_e / [Na]_i$ ratios showed only numerical changes in skeletal and car-

diac muscle. The intracellular Cl concentration decreased significantly in red cells in both series and in the cardiac muscle in the 60G-series. The $[Cl]_e / [Cl]_i$ ratio decreased significantly in white skeletal muscle in the 12G-series and increased significantly in the cardiac muscle in the 60G-series. Otherwise

only numerical changes in this ratio were noted. The intracellular oedema thus seem to have but little effect on the Na-K transport. The water intoxication thus had surprisingly small effect on the active electrolyte-fluid distribution within the mammalian body.

SUMMARY

The effect of nephrectomy and nephrectomy plus overhydration with 0.9% saline or 3% glucose solution on the electrolyte-fluid distribution and on some circulatory variables was studied in 193 white male rabbits weighing 1.6–2.6 kg. The water, Na, K and Cl content of the total body and various tissues were determined. The extracellular space was estimated by means of ^{82}Br and ^{51}Cr -EDTA and from endogenous Cl. ^{51}Cr -EDTA was found to be an acceptable extracellular marker for the skeletal and cardiac muscle and apparently also for the stomach, but not for the other tissues examined. Some of the animals were analysed at 12, 36, 60 and 84 hrs after nephrectomy in order to investigate the relationship between the interval after the loss of kidney function and the variables under study. The rest of the animals were overhydrated to 5, 10, 15 and 20 percent of their bodyweight with the saline or the glucose solution immediately (the 12S and 12G-series) or 48 hrs (the 60S and 60G-series) after nephrectomy. The animals were analysed 12 hrs after the beginning of the overhydration. This part of the investigation was undertaken to obtain a conception of the distribution of water and electrolytes at different degrees of iso-osmotic and hypo-osmotic overhydration at different time intervals after nephrectomy.

The period studied after nephrectomy could be divided into two phases.

During the initial phase (the first 12 hrs) after nephrectomy the following main changes were observed: TBK increased and probably also TBNa and TBW, while TBCl and TBS were unchanged. The presumed Na-excess was distributed mainly to the extracellular volume, which seemed to increase. The K-excess was distributed both to the extra and intracellular volume. The latter seemed also to increase somewhat. The plasma and red cell volume increased considerably.

The intracellular amount of water increased in skeletal muscle, while it was unchanged in cardiac muscle.

The intracellular K-content and concentration increased or tended to increase in skeletal and cardiac muscle and in red cells. The intracellular Na and Cl

content and concentration showed only minor changes in skeletal and cardiac muscle and in red cells during this period.

The plasma Na concentration was unchanged, while that of K, Ca and Mg increased considerably. The plasma Cl, inorganic phosphorus and HCO_3 concentration tended to decrease.

The blood pressure, the central venous pressure and the heart rate seemed to increase, while the roentgenologic heart size seemed to decrease.

During the second phase (12–84 hrs) after nephrectomy the following main changes were observed: The animals got an increasing azotaemia, hypothermia and metabolic acidosis.

TBW, TBS, TBNa and TBK decreased, while TBCl was unchanged. ECW seemed to increase somewhat, while ICW decreased. The plasma and red cell volume decreased somewhat. A considerable part of the decrease in TBW, TBS, TBNa, TBK and ICW could be ascribed to the intraluminal compartment of the intestines, and the rest mainly to the skin and the eviscerated body. The amount of water and solids in the heart and in the lungs increased. The interstitial space of the stomach increased considerably.

The intracellular amount of water increased hyperbolically in skeletal muscle and was unchanged in cardiac muscle.

The intracellular amount of K increased hyperbolically in skeletal muscle, without any change in the intracellular K concentration. The intracellular K content and concentration decreased in red cells, which also seemed to be true for cardiac muscle. The intracellular Na and Cl content and concentration increased or tended to increase in skeletal muscle and red cells. In cardiac muscle the intracellular Cl content and concentration also increased, but in this tissue the intracellular Na content and concentration seemed to decrease.

The plasma Na, Ca, Cl and HCO_3 concentrations decreased while the plasma K and Mg concentrations increased hyperbolically and that of inorganic phosphorus increased more linearly. No significant liberation of Na from the bone could be registered.

The blood pressure continued to increase, while the central venous pressure, the heart rate and the roentgenologic heart size were unchanged. This was somewhat astonishing, since renoprival hypertension has been denied to occur in the rabbit.

Saline overhydration caused the following principle changes: ECW seemed to increase more than the amount of water infused, especially in the 12S-series. The red cell volume was unchanged, and the plasma volume seemed to increase hyperbolically.

A mild dehydration seemed to have occurred in the skeletal muscle, while the intracellular amount of water increased in cardiac muscle.

The water, Na and Cl excess was mainly distributed to the skin, to the eviscerated body and to the peritoneal cavity. The amount of fluid in the peritoneal cavity increased more in the 12S than in the 60S-series, while the reverse was true for the stomach. The relative increase in the amount of water was largest for the skin in both series, with the exception of the stomach in the 60S-series. The latter large increase could be ascribed to uraemic gastritis.

The intracellular K content decreased somewhat, while the intracellular K concentration was unchanged in skeletal muscle. No changes in these two variables could be observed in cardiac muscle or red cells.

The red cell Na concentration increased considerably in the 12S-series and the intracellular Na concentration tended to increase in red skeletal muscle in the 60S-series. The red cell Cl concentration increased in both series, while the intracellular Cl concentration tended to decrease in white skeletal muscle in the 60S-series. Otherwise no remarkable changes could be found in the intracellular Na and Cl contents or concentrations.

The plasma Na concentration increased numerically and significantly in the 12S and 60S-series, respectively. The plasma K and Mg concentration decreased in the 60S-series, while it was unchanged in the 12S-series.

The plasma Ca concentration was unchanged in the 12S-series and seemed to increase in the 60S-series. The plasma Cl concentration increased considerably, while that of inorganic phosphorus was unchanged. No significant dilution acidosis could be observed.

The blood pressure and the heart rate were un-

changed, while the central venous pressure and the roentgenologic heart size increased, the former hyperbolically.

Glucose overhydration caused the following main changes: The determined relative increase of ECW was considerably larger than that of ICW, especially in the 12G-series. Whether this held also for the true ECW and ICW could not with certainty be decided, but much favoured the view that it did not. The plasma volume seemed to increase hyperbolically, as in the saline overhydrated series and the red cell volume was unchanged in spite of osmotic hemolysis.

The water excess was more evenly distributed in the body in the glucose than in the saline overhydrated series. No remarkable difference could be found in the distribution pattern of the water excess between the 12G and the 60G-series.

The increase in the water content of the brain tissue was small compared with that of most of the other tissues examined. This was osmotically possible because the brain tissue lost Na, Cl and K.

The intracellular K content of red skeletal muscle decreased in the 60G-series. The intracellular Na content of cardiac muscle tended to decrease in both series. The intracellular Cl content of cardiac muscle decreased in the 60G-series.

The red cell K and Cl concentration decreased in both series, as well as the red cell Na concentration in the 60G-series. In the 12G-series the latter decreased only numerically. The intracellular K concentration decreased considerably in skeletal and cardiac muscle.

The intracellular Na concentration decreased in cardiac muscle in both series and in red skeletal muscle in the 12S-series. The intracellular Cl concentration of cardiac muscle decreased. Otherwise no remarkable changes could be observed in the intracellular Na and Cl contents or concentrations.

The plasma Na and Cl concentrations fell considerably. No significant liberation of Na from the skeleton could be demonstrated. The plasma K and Mg concentrations were unchanged in the 12G-series, while they fell in the 60G-series. Plasma inorganic phosphorus concentration was unchanged or tended to increase. The acid base status was unchanged.

The circulation variables determined changed largely in the same way as in the saline overhydrated series.

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APPENDIX

Series	Nr of animals	BW ₀ Mean	(kg) range	PV nr. of determination	Microscopic findings in the lungs				
					0	(+)	+	++	+++
Controls	9	1.99	1.68—2.39	9	8	1	—	—	—
12 hrs	17	1.98	1.66—2.32	5	8	9	—	—	—
36 hrs	10	2.18	1.71—2.40	5	4	4	2	—	—
60 hrs	17	2.01	1.71—2.48	9	2	8	8	—	—
84 hrs	14	1.98	1.70—2.39	5	—	4	10	—	—
12S5	10	2.09	1.66—2.30	4	—	9	1	—	—
12S10	11	2.04	1.78—2.35	4	—	10	1	—	—
12S15	15	2.05	1.63—2.38	5	—	10	5	—	—
12S20	3	1.99	1.86—2.18	5	1	2	—	—	—
12G5	10	2.04	1.75—2.37	5	—	3	7	—	—
12G10	10	2.15	1.67—2.60	5	2	5	3	—	—
12G15	16	2.02	1.67—2.44	5	1	6	9	—	—
12G20	3	2.01	1.71—2.28	3	—	2	1	—	—
60S5	6	1.97	1.82—2.27	6	1	1	4	—	—
60S10	5	1.96	1.76—2.12	5	1	1	2	1	—
60S15	11	2.03	1.66—2.63	10	—	5	5	1	—
60S20	3	2.22	2.12—2.36	3	—	—	—	3	—
60G5	5	2.10	1.83—2.30	5	—	1	4	—	—
60G10	5	1.94	1.87—2.09	4	—	2	3	—	—
60G15	11	2.06	1.66—2.42	10	—	6	5	—	—
60G20	2	2.24	2.05—2.43	2	—	1	1	—	—
Total	193	2.04	1.63—2.63	112	28	89	71	5	—

Number of animals in the different experimental groups and the mean and range of their body weight at the start of the experiments (BW₀). The number of animals in which the plasma volume were determined and the results of the microscopic examination of the lungs. (O=no alveoli filled with protein precipitate per 10 fields of vision; (+)=1—2; +=2—5; ++=6—10; +++=>10).

Effect of nephrectomy and nephrectomy plus overhydration on the variables studied (see text and fig. 1–18). In the tables the means $\pm$ SE are given for the control, 12 hr and 60 hr series. The significant and nearly significant (within brackets) b-values of the linear regression equation (i.e. the change per 24 hrs or percent overhydration) for the different variables are included. The significance of the mean difference between the control and the 12 hr series are given, as well as the significance of the difference between the b-values of the overhydrated series.

(Values forming basis of fig. 1)

	Controls M $\pm$ SE	12hr M $\pm$ SE	Diff. C-12hr p <	12	84hr	b-values 12S	12G	60hr M $\pm$ SE	60S	b-values 60G	12S-G	Diff. 60S-G	b-values S12-60	p <
temp.	39.5 $\pm$ 0.25	38.8 $\pm$ 0.16	0.025	—	—0.71	(-0.031)	-0.062	37.1 $\pm$ 0.26	—	—	—	—	—	—
resp. rate	123 $\pm$ 9	108 $\pm$ 5	—	—	-9.3	—	—	97 $\pm$ 16	—	(-1.4)	—	—	—	—
heart rate	198 $\pm$ 11	228 $\pm$ 12	—	—	—	—	—	208 $\pm$ 13	—	—	—	—	—	—
BP	97 $\pm$ 3.3	106 $\pm$ 2.5	0.05	—	+4.6	—	—	119 $\pm$ 3.3	—	—	—	—	—	—
CVP	3.9 $\pm$ 0.45	6.3 $\pm$ 0.47	0.005	—	—	—	(+0.12)	5.5 $\pm$ 0.50	$\pm$ 0.21	+0.23	—	—	—	—
HVI	4.6 $\pm$ 0.13	4.0 $\pm$ 0.18	0.05	—	—	+0.053	+0.087	4.2 $\pm$ 0.14	(+0.043)	+0.065	—	—	—	—

(Values forming basis of figs. 2 and 3)

creat/p	0.9 $\pm$ 0.04	4.1 $\pm$ 0.19	0.001	—	$\pm$ 2.4	—	—	9.2 $\pm$ 0.44	—	-0.14	—	—	—	—
urea-N/p	14 $\pm$ 1.7	34 $\pm$ 2.5	0.001	—	+55.3	—	—	169 $\pm$ 9.4	(-1.7)	-2.7	—	—	—	—
osm.	299 $\pm$ 2.2	295 $\pm$ 2.3	—	—	+26.0	$\pm$ 0.92	2.42	371 $\pm$ 7.8	-1.67	-5.58	0.001	0.001	—	—
Hb	10.2 $\pm$ 0.21	10.9 $\pm$ 0.29	—	—	(0.32)	—	-0.13	9.9 $\pm$ 0.23	-0.070	-0.10	—	—	—	—
hct	35.1 $\pm$ 0.52	40.7 $\pm$ 1.65	0.025	—	(1.81)	(-0.28)	-0.47	32.2 $\pm$ 0.48	—	(-0.15)	—	—	—	—
P.P.	5.7 $\pm$ 0.22	5.6 $\pm$ 0.12	—	—	+0.20	-0.043	(-0.030)	6.2 $\pm$ 0.11	-0.058	-0.065	—	—	—	—
blood gluc.	100 $\pm$ 4.5	109 $\pm$ 3.8	—	—	—	-1.39	—	113 $\pm$ 7.0	(1.29)	(+1.90)	—	0.005	—	—

(Values forming basis of figs. 3 and 4)

[Na] _p	143 $\pm$ 1.3	144 $\pm$ 0.9	—	—	-2.15	—	-1.75	136 $\pm$ 1.7	+0.50	-1.40	0.001	0.001	—	—
[K] _p	3.9 $\pm$ 0.14	5.3 $\pm$ 0.22	0.001	—	+0.89	—	—	8.6 $\pm$ 0.39	-0.14	-0.09	—	—	—	—
[Cl] _p	104 $\pm$ 1.3	100 $\pm$ 1.1	0.05	—	(1.19)	+0.85	-1.59	96 $\pm$ 1.0	+0.98	-1.32	0.001	0.001	—	—
[Ca] _p	6.6 $\pm$ 0.11	8.2 $\pm$ 0.36	0.005	—	1.35	—	-0.10	4.2 $\pm$ 0.26	(+0.053)	—	—	—	—	—
[P] _p	2.3 $\pm$ 0.12	1.8 $\pm$ 0.13	0.02	—	+0.41	—	(+0.024)	2.7 $\pm$ 0.18	—	—	—	—	—	—
[Mg] _p	2.2 $\pm$ 0.09	3.4 $\pm$ 0.19	0.001	—	—	—	—	4.1 $\pm$ 0.15	0.041	-0.083	—	0.05	—	—
pH	7.41 $\pm$ 0.016	7.37 $\pm$ 0.018	—	—	-0.044	—	—	7.28 $\pm$ 0.023	—	—	—	—	—	—
St.HCO ₃	24.1 $\pm$ 1.0	21.7 $\pm$ 1.3	—	—	-2.40	—	—	16.1 $\pm$ 1.0	—	—	—	—	—	—
B.E.	0.2 $\pm$ 1.3	-3.1 $\pm$ 1.6	—	—	-3.32	(-0.27)	—	-10.9 $\pm$ 1.5	—	—	—	—	—	—
pCO ₂	37.6 $\pm$ 1.5	37.4 $\pm$ 1.6	—	—	-2.15	-0.38	—	31.7 $\pm$ 1.3	—	—	—	—	—	—

Red cells (Values forming basis of fig. 5)

[Na] _{rc}	13.4 $\pm$ 0.5	10.9 $\pm$ 0.6	0.02	—	(+1.5)	+0.31	—	17.6 $\pm$ 1.1	—	-0.32	0.001	0.02	—	—
[K] _{rc}	109 $\pm$ 2.2	117 $\pm$ 2.1	0.025	—	7.0	—	-2.0	102 $\pm$ 2.4	—	-2.1	0.001	0.001	—	—
Br _{rc}	0.473 $\pm$ 0.013	0.526 $\pm$ 0.048	—	—	+0.037	—	—	0.609 $\pm$ 0.015	—	—	—	—	—	—

Free body fluids (Values forming basis of fig. 6)

	Controls M±SE	12hr M±SE	Diff. C-12hr p<	12-84hr	b-values 12S	12G	60hr M±SE	b-values		12S-G	Diff. 60S-G	b-values S12-60 G12-60 p<
								60S	60G			
asc.fl.	2.4±0.12	1.2±0.50	—	—	+1.66	+0.59	4.4±1.08	+0.87	+0.45	0.001	—	—
pl.eff.	0.67±0.13	0.64±0.08	—	—	+0.130	+0.050	0.87±0.14	+0.104	+0.067	0.001	—	0.01
per.eff.	0.30±0.04	0.17±0.03	0.02	—	—	—	0.30±0.06	—	—	—	—	—
FBF												
Na	0.53±0.18	0.29±0.08	—	—	+0.28	+0.074	0.83±0.16	+0.15	+0.075	0.001	0.05	0.01
K	0.023±0.008	0.011±0.003	0.05	—	+0.011	+0.041	0.053±0.012	+0.0057	—	0.001	—	0.01
C1	0.38±0.14	0.21±0.06	—	—	+0.23	+0.051	0.61±0.12	+0.13	+0.032	0.001	0.005	0.01

Skin (Values forming basis of fig. 7)

Weight	169±2.8	160±2.2	0.025	—	+4.4	+2.5	174±2.2	+4.4	+2.5	0.001	0.001	—
FFS	56±0.8	53±1.2	—	—	—	—	58±1.6	—	—	—	—	—
H ₂ O	105±3.1	101±1.8	—	3.8	+3.9	+1.8	102±2.3	+4.0	+2.5	0.001	0.005	—
ECW _B	87±1.5	86±3.8	—	—	+3.6	+1.8	94±2.3	+3.4	+1.7	0.001	0.001	—
ECW _{Br}	98±2.7	94±2.5	—	—	+4.8	+3.2	114±4.2	+4.1	+2.4	0.001	0.01	—
ECW _{Cr}	78±2.7	78±2.7	—	—	+4.3	+2.4	91±2.1	+4.2	+2.5	0.001	0.001	—
PV	3.5±0.2	5.6±1.3	—	—	—	—	5.5±0.4	—	—	—	—	—
Na	17.3±0.3	17.6±0.3	—	−0.62	+0.54	—	17.7±0.6	+0.61	—	0.001	—	—
K	6.0±0.2	6.4±0.2	—	−0.34	—	—	6.3±0.2	—	—	—	—	—
C1	9.9±0.1	9.4±0.4	—	—	+0.54	—	10.0±0.3	+0.52	—	0.001	0.001	—

Gastric contents (Values forming basis of fig. 8)

Weight	25.8±3.4	37.4±2.6	0.02	8.2	—	—	19.9±4.9	—	—	—	—	—
DV _{Br}	33.2±5.1	54.1±4.0	0.005	−11.9	(−0.9)	—	30.0±2.2	—	0.01	—	—	—
DV _{Cr}	0.6±0.1	1.3±0.2	0.025	—	—	—	2.4±1.3	—	—	—	—	—

Stomach (values forming basis of fig 9.)

Weight	15.5±0.5	14.5±0.5	—	+1.1	—	(+0.10)	17.7±0.2	+0.51	—	—	0.01	0.001
FFS	2.6±0.1	2.3±0.1	0.02	—	—	—	2.5±0.1	—	—	—	—	—
H ₂ O	12.0±0.3	11.4±0.4	—	+1.1	(+0.06)	+0.12	14.8±0.6	+0.31	—	—	—	0.01
DV _{Cr}	7.3±0.4	8.8±0.4	0.025	+1.3	—	+0.14	11.3±0.6	+0.36	(+0.13)	—	0.02	0.001
DV _{Br}	8.3±0.4	9.5±0.5	—	+1.4	—	+0.17	12.4±0.6	+0.40	(+0.17)	—	0.05	0.001
DV _{Cr}	4.0±0.2	4.0±0.2	—	+1.4	+0.11	+0.10	7.3±0.7	+0.43	(+0.17)	—	0.02	0.001
PV	0.38±0.01	0.44±0.07	—	—	—	—	0.42±0.04	—	—	—	—	—
Na	0.54±0.02	0.50±0.02	—	+0.16	+0.011	—	0.82±0.07	+0.050	—	0.02	0.001	0.001
K	0.85±0.05	0.86±0.03	—	—	—	—	0.86±0.03	(+0.010)	—	—	0.05	—
C1	0.76±0.03	0.92±0.06	—	+0.10	(+0.009)	—	1.08±0.05	+0.044	0.001	0.001	0.001	0.001

	Controls M $\pm$ SE	12hrs M $\pm$ SE	Diff. p<	12-82hrs	b-values 12S	12G	60hrs M $\pm$ SE	b-values 60S	b-values 60G	12S-G	Diff. 60S-G	b-values S12-60 G12-60 p<
<i>Intestinal preparation (Values forming basis of fig. 10)</i>												
Weight	154 $\pm$ 7.5	146 $\pm$ 5.4	—	—	—	—	—	—	—	—	—	—
FFS	27.9 $\pm$ 1.6	27.2 $\pm$ 1.0	—	-16.8	—	+2.1	125 $\pm$ 4.5	—	+1.3	0.025	0.02	—
H ₂ O	125 $\pm$ 6.6	117 $\pm$ 4.8	—	-4.0	—	—	21.0 $\pm$ 1.0	0.25	—	—	—	—
DV ₁ C1	48.3 $\pm$ 3.3	46.0 $\pm$ 3.0	—	-12.8	—	+1.9	104 $\pm$ 4.2	—	(+1.2)	0.05	—	—
DV ₂ Br	48.8 $\pm$ 3.6	49.2 $\pm$ 3.1	—	—	+0.9	+1.0	47.4 $\pm$ 3.0	—	—	—	—	—
DV ₂ Cr	48.9 $\pm$ 2.6	48.7 $\pm$ 3.9	—	—	+1.0	+1.0	49.9 $\pm$ 3.1	(+0.7)	—	—	—	—
PV	2.4 $\pm$ 0.15	3.7 $\pm$ 0.29	0.001	—	+1.2	+0.9	68.4 $\pm$ 4.6	—	+1.8	—	0.01	—
Na	10.4 $\pm$ 1.3	11.1 $\pm$ 0.5	—	-1.2	—	—	3.2 $\pm$ 0.28	—	—	—	—	—
K	9.5 $\pm$ 0.5	9.7 $\pm$ 0.3	—	0.6	—	(-0.09)	9.9 $\pm$ 0.6	—	—	—	—	—
Cl	5.0 $\pm$ 0.3	5.1 $\pm$ 0.6	—	—	+0.15	+0.10	9.7 $\pm$ 0.3	—	—	—	—	—
			—	—	—	—	4.5 $\pm$ 0.3	+0.10	—	0.001	0.01	—
<i>Liver (Values forming basis of fig. 11)</i>												
Weight	44.9 $\pm$ 2.6	44.4 $\pm$ 1.3	—	—	—	—	—	—	—	—	—	—
Solids	11.2 $\pm$ 0.7	10.5 $\pm$ 0.4	—	—	—	+0.86	48.3 $\pm$ 2.1	—	+0.58	0.001	0.05	—
H ₂ O	33.7 $\pm$ 2.0	34.0 $\pm$ 1.0	—	—	—	(+0.16)	11.5 $\pm$ 0.4	—	—	—	—	—
DV ₁ C1	13.1 $\pm$ 0.7	13.9 $\pm$ 0.7	—	—	—	+0.70	37.3 $\pm$ 2.2	—	(+0.35)	0.001	—	—
DV ₂ Br	16.2 $\pm$ 0.8	16.8 $\pm$ 0.8	—	—	—	+0.26	16.2 $\pm$ 0.9	—	—	0.05	—	—
DV ₂ Cr	27.9 $\pm$ 2.0	30.1 $\pm$ 1.5	—	—	—	+0.27	18.8 $\pm$ 1.0	—	(+0.19)	0.05	—	—
PV	8.7 $\pm$ 0.40	9.6 $\pm$ 0.80	—	-2.7	—	—	25.0 $\pm$ 1.3	—	—	—	—	—
Na	2.30 $\pm$ 0.10	2.30 $\pm$ 0.11	—	—	—	—	11.7 $\pm$ 1.0	—	(+0.20)	—	—	—
K	3.25 $\pm$ 0.20	3.32 $\pm$ 0.10	—	—	—	—	2.74 $\pm$ 0.14	—	(-0.023)	—	0.025	—
Cl	1.36 $\pm$ 0.06	1.40 $\pm$ 0.07	—	—	(+0.014)	—	3.35 $\pm$ 0.21	—	—	—	—	—
			—	—	—	—	1.60 $\pm$ 0.08	+0.023	(-0.014)	0.05	0.001	—
<i>Spleen</i>												
Weight	0.46 $\pm$ 0.066	0.48 $\pm$ 0.033	—	-0.053	—	—	0.33 $\pm$ 0.028	—	—	—	—	—
DV ₂ Br	0.17 $\pm$ 0.023	0.18 $\pm$ 0.013	—	0.018	—	—	0.13 $\pm$ 0.010	—	—	—	—	—
DV ₂ Cr	0.15 $\pm$ 0.022	0.18 $\pm$ 0.011	—	(-0.016)	—	—	0.14 $\pm$ 0.015	—	—	—	—	—
PV	0.036 $\pm$ 0.004	0.057 $\pm$ 0.014	—	—	—	—	0.042 $\pm$ 0.005	—	—	—	—	—
<i>Lungs (Values forming basis of fig. 12)</i>												
Weight	7.4 $\pm$ 0.52	6.3 $\pm$ 0.24	0.05	(+0.30)	—	+0.081	7.9 $\pm$ 0.28	—	—	—	—	—
Solids	1.24 $\pm$ 0.04	1.17 $\pm$ 0.05	—	(+0.048)	—	—	1.40 $\pm$ 0.04	—	—	—	—	—
H ₂ O	6.1 $\pm$ 0.24	5.2 $\pm$ 0.20	0.02	(+0.25)	—	+0.080	6.5 $\pm$ 0.24	—	—	—	—	—
DV ₂ C1	4.6 $\pm$ 0.20	3.9 $\pm$ 0.15	0.02	+0.34	—	+0.065	5.2 $\pm$ 0.23	—	—	—	—	—
DV ₂ Br	5.3 $\pm$ 0.25	4.5 $\pm$ 0.24	0.05	+0.30	—	+0.078	5.8 $\pm$ 0.25	—	—	—	—	—
DV ₂ Cr	4.2 $\pm$ 0.16	3.6 $\pm$ 0.19	0.05	+0.51	—	+0.055	4.5 $\pm$ 0.19	—	—	—	—	—
PV	2.7 $\pm$ 0.22	2.9 $\pm$ 0.35	—	—	—	—	3.2 $\pm$ 0.22	—	—	—	—	—
Na	0.62 $\pm$ 0.026	0.51 $\pm$ 0.020	0.005	+0.037	(+0.0055)	—	0.67 $\pm$ 0.028	—	(-0.0059)	—	0.02	—
K	0.44 $\pm$ 0.023	0.41 $\pm$ 0.020	—	—	—	—	0.42 $\pm$ 0.014	—	—	—	—	—
Cl	0.47 $\pm$ 0.017	0.39 $\pm$ 0.014	0.005	+0.026	+0.0066	—	0.49 $\pm$ 0.020	+0.0083	(-0.0043)	0.005	0.001	—

Brain (Values forming basis of fig. 13)

	Controls M±SE	12hr M±SE	Diff: C-12hr p<	12-84hr	b-values 12S	12G	60hr M±SE	b-values 60S	60G	12S-G	Diff: 60S-G p<	b-values S12-60 G12-60 p<
H ₂ O _m	382±5.1	396±4.3	—	(-5.2)	—	+1.4	380±5.1	—	+1.9	0.001	—	—
DV _{Cl} _m	181±2.9	208±2.6	0.001	+4.0	-0.78	—	211±2.5	-0.81	—	0.01	—	—
DV _{Br} _m	112±2.6	132±2.6	0.001	+3.7	(-0.56)	+0.64	134±1.5	—	—	0.001	—	—
DV _{Cr} _m	12.1±0.81	14.4±0.95	—	—	—	—	14.3±0.82	(+0.13)	—	—	—	—
PV _m	4.7±0.34	5.0±0.30	—	—	—	—	4.8±0.30	—	—	—	—	—
Na _m	30.3±0.56	32.3±0.44	0.02	—	—	-0.28	30.3±0.31	(+0.092)	-0.22	0.001	0.001	—
K _m	45.5±0.90	47.4±0.31	0.025	—	—	-0.24	45.7±0.67	(+0.13)	(-0.14)	0.001	0.001	—
Cl _m	18.7±0.27	20.8±0.32	0.001	—	—	-0.30	20.2±0.23	+0.12	-0.27	0.001	0.001	—

Heart

Weight	2.12±0.11	1.98±0.07	—	+0.11	—	—	2.48±0.06	—	—	—	—	—
FFS	0.45±0.02	0.40±0.02	—	+0.024	—	—	0.52±0.01	—	—	—	—	—
H ₂ O	1.64±0.10	1.56±0.05	—	+0.078	—	—	1.93±0.05	—	—	—	—	—
Na	0.102±0.006	0.094±0.004	—	—	—	—	0.111±0.004	—	-0.00112	—	0.001	—
K	0.176±0.011	0.165±0.007	—	(+0.0055)	—	—	0.202±0.006	—	—	—	—	—
Cl	0.069±0.003	0.065±0.002	—	+0.0013	+0.00082	-0.00078	0.082±0.003	+0.00070	-0.00126	0.001	0.001	0.05

Cardiac muscle (Values forming basis of fig 14)

H ₂ O _m	375±4.6	387±6.2	—	—	—	+2.30	375±4.5	—	+2.16	0.01	0.005	—
H ₂ O _{Cr}	113±5.1	121±4.0	—	—	—	+0.86	116±2.8	—	+0.79	0.01	0.01	—
H ₂ O _{Cr}	249±4.5	244±4.1	—	—	+0.95	+1.75	247±3.0	(+0.54)	+1.43	—	0.025	—
PV _m	34.9±1.0	40.9±2.3	—	—	—	—	35.5±1.3	—	—	—	—	—
Na _m	22.9±1.5	23.4±0.6	—	(-0.56)	—	-0.19	21.3±0.5	—	-0.17	0.001	0.001	—
[Na] _i	6.2±0.6	5.3±0.6	—	—	—	(-0.098)	4.9±0.4	—	(-0.080)	0.02	0.02	—
[Na] _i	24.7±2.2	21.4±2.3	—	—	—	-0.50	19.8±1.3	—	-0.40	0.001	0.01	—
K _m	36.6±0.7	40.9±0.6	0.001	-0.89	—	-0.17	38.8±0.6	—	—	0.001	—	—
K _i	34.1±0.7	36.9±0.6	0.01	(-0.57)	—	—	36.1±0.6	—	—	—	—	—
[K] _i	137±2.0	152±2.7	0.005	—	—	-1.36	146±2.2	—	-0.81	0.001	0.001	—
Cl _m	15.5±0.4	16.2±0.4	—	—	+0.18	-0.20	15.6±0.5	+0.11	-0.21	0.001	0.001	—
Cl _i	1.8±0.4	1.6±0.3	—	(+0.064)	(+0.064)	—	2.6±0.3	—	0.095	0.02	0.025	—
[Cl] _i	7.1±1.6	5.7±1.3	—	—	(+0.28)	—	10.3±1.1	—	-0.40	0.02	0.02	—

White skeletal muscle (Values forming basis of fig. 15)

	Controls M±SE	12hr M±SE	Diff. C-12hr p<	12-84hr	b-values 12S	12G	60hr M±SE	b-values 60S	b-values 60G	12S-G	Diff. 60S-G	b-values S12-60 G12-60 p<
H ₂ O _m	331±3.0	341±4.2	—	—	(+0.89)	+5.92	353±6.3	—	+4.60	0.001	0.001	—
H ₂ O _e	31.4±1.1	37.7±2.7	—	—	+1.15	+0.99	36.6±2.1	—	(+0.41)	—	—	—
H ₂ O _i	300±3.3	304±2.5	—	—	—	+4.67	316±4.6	—	+3.76	0.001	0.001	—
Na _m	6.26±0.25	7.56±0.41	0.05	—	+0.201	(+0.095)	7.49±0.35	(-0.084)	—	0.05	—	—
Na _i	1.76±0.23	1.98±0.12	—	—	—	—	2.51±0.17	—	—	—	—	—
[Na] _i	6.2±0.88	7.0±0.59	—	—	—	—	7.9±0.48	—	—	—	—	—
K _m	50.6±0.4	52.2±0.6	—	—	(-0.12)	—	55.0±0.8	(-0.15)	—	—	—	—
K _i	50.5±0.4	51.8±0.6	—	—	-0.14	—	54.7±0.8	(0.15)	—	—	—	—
[K] _i	168±1.1	171±1.4	—	—	—	-1.91	173±1.4	—	-1.85	0.001	0.001	—
Cl _m	4.17±0.10	5.13±0.28	0.025	—	+0.194	(+0.061)	5.50±0.22	-0.071	—	0.001	0.05	—
Cl _i	0.57±0.13	0.91±0.09	0.05	+0.26	—	—	1.90±0.13	—	—	—	—	—
[Cl] _i	1.9±0.42	3.0±0.32	—	+0.85	—	—	5.8±0.35	-0.12	—	—	—	—
PV _m	1.0±0.1	2.5±0.1	0.001	—	—	—	1.9±0.1	—	—	—	—	—

Red skeletal muscle (Values forming basis of fig. 16)

H ₂ O _m	349±3.3	367±4.7	0.02	—	—	+4.90	385±7.6	—	+2.56	0.001	0.001	0.01
H ₂ O _e	35.6±3.1	46.6±3.1	0.05	—	(+0.51)	—	45.2±2.7	—	—	—	—	—
H ₂ O _i	312±1.8	319±3.1	—	—	—	+4.61	339±5.7	—	+2.19	0.001	0.001	0.01
Na _m	8.2±0.33	9.5±0.42	0.05	—	(+0.094)	—	9.31±0.47	(+0.11)	—	—	—	—
Na _i	3.1±0.33	2.7±0.21	—	—	—	—	3.14±0.24	—	—	—	—	—
[Na] _i	9.8±1.05	8.4±0.62	—	—	—	-0.15	9.2±0.67	(+0.16)	—	0.05	0.05	—
K _m	50.7±0.7	54.1±0.7	0.005	—	(-0.14)	—	57.5±0.8	-0.24	-0.29	—	—	0.01
K _i	50.6±0.6	53.8±0.7	0.01	—	-0.14	—	57.1±0.8	-0.23	-0.29	—	—	0.01
[K] _i	162±1.4	169±1.7	0.02	—	—	-1.93	169±2.1	—	-1.78	0.001	0.001	—
Cl _m	5.4±0.12	6.5±0.31	0.02	—	+0.11	—	6.98±0.39	(+0.07)	—	0.001	0.02	—
Cl _i	1.28±0.20	1.40±0.16	—	(+0.26)	—	—	3.83±1.66	—	—	—	—	—
[Cl] _i	4.1±0.64	4.4±0.48	—	+0.72	—	—	6.5±0.57	—	—	—	—	—
PV _m	2.0±0.2	3.2±0.1	0.001	—	—	—	3.6±0.2	—	—	—	—	—

SM-preparation (Values forming basis of fig. 17)

	Controls M±SE	12hr M±SE	Diff. C-12hr p <	12-84hr	b-values 12S	12G	60hr M±SE	b-values 60S	60G	12S-G	Diff. 60S-G	b-values SI2-60 p <	G12-60
Weight	493±9.0	526±6.4	0.01	—	+3.1	+3.3	559±6.8	+3.2	+4.2	—	—	—	—
FFS	117±2.2	124±1.9	0.05	(-2.6)	—	(-0.40)	129±2.8	—	—	—	—	—	—
H ₂ O	352±4.1	375±3.6	0.001	—	+3.0	+3.6	402±4.9	+3.1	+4.1	—	—	—	—
ECW _{Cl}	118±2.1	131±2.5	0.001	—	+3.4	+2.1	152±2.4	+3.1	+1.9	0.001	0.01	—	—
ECW _{Br}	113±3.2	129±0.3	0.001	—	+3.6	+2.2	153±3.8	+3.0	+1.7	0.001	0.01	—	—
ECW _{Cr}	114±3.6	117±2.4	—	—	+3.8	+2.4	138±3.8	+3.1	+1.4	0.001	0.001	—	—
ICW _{Cr}	237±6.5	258±4.2	0.01	-9.7	—	+1.5	264±6.2	—	+3.0	0.001	0.001	—	—
PV	15.0±0.43	22.6±1.71	0.001	—	—	—	21.7±1.32	—	—	—	—	—	—
Na	23.5±0.46	26.5±0.32	0.001	—	+0.61	—	28.0±0.57	+0.57	-0.12	0.001	0.001	—	—
K	40.7±0.92	44.0±0.67	0.01	-1.4	—	-0.26	45.4±1.13	—	—	—	—	—	—
Cl	13.6±0.24	15.3±0.27	0.001	—	+0.58	(-0.08)	16.6±0.27	+0.54	—	0.001	0.001	—	—

Total body (Values forming basis of fig. 18)

BW _A	961±5.9	978±2.8	0.01	-33.0	+9.2	+9.7	986±1.4	+9.1	+9.9	—	0.02	—	—
TBS	217±2.0	219±2.7	—	-6.6	—	—	225±3.5	—	—	—	—	—	—
TBF	31.0±5.4	29.8±2.3	—	—	—	—	37.9±2.6	—	—	—	—	—	—
TBW	649±6.1	659±4.4	—	-18.6	+9.2	+9.0	686±7.0	+8.7	+8.9	—	—	—	—
ECW _{Cl}	278±5.6	283±5.2	—	—	+10.1	+6.2	324±10.3	+9.0	+5.4	0.001	0.001	—	—
ECW _{Br}	260±10.5	291±4.8	0.001	—	+10.9	+7.1	347±9.8	+9.0	+5.0	0.001	0.001	—	—
ECW _{Cr}	—	261±7.6	—	—	+11.7	+7.4	337±11.3	+10.0	+5.9	0.001	0.01	—	—
ICW _{Cr}	—	398±8.0	—	-25	2.4	+1.8	346±8.7	—	+2.9	0.001	0.001	—	—
PV _B	41.8±0.8	57.4±4.7	0.005	—	—	—	55.2±2.4	—	—	—	—	—	—
RCV _B	20.8±0.4	25.9±1.5	0.005	-2.2	—	—	22.7±1.1	—	—	—	—	—	—
BV _B	62.6±1.0	83.4±6.0	0.001	(-4.5)	—	—	77.9±3.4	—	—	—	—	—	—
TBNa	57.0±0.9	59.8±0.9	—	-1.7	+1.56	—	61.6±0.9	+1.37	—	0.001	0.001	—	—
TBK	61.8±0.7	65.8±0.6	0.001	-2.5	—	(-0.19)	67.4±0.9	—	—	—	—	—	—
TBCl	32.8±0.6	33.3±0.8	—	—	+1.50	—	35.6±1.0	+1.41	—	0.001	0.001	—	—

